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A CLINICAL STUDY OF PNEUMONIA BASED ON EIGHT HUNDRED AND SEVENTY-ONE CASES*

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INTRODUCTION

Only completed cases of pneumonia treated at the U. S. Army Base Hospital, Fort Riley, Kan., during the seven months' period, Oct. 18, 1917, to May 18, 1918, are included in this report (Fig. 1). This series is made up of 668 instances of lobar pneumonia, 181 instances of measles pneumonia,[1] and 22 instances of bronchopneumonia. During the period, Oct. 1, 1917, to May 18, 1918, there were 22,854 admissions, making a total incidence for pneumonia of 4.5 per cent. Of the 668 completed instances of lobar pneumonia, 154 patients died, a mortality of 23 per cent. Of these 154 deaths, 87 were complicated by empyema. The mortality of lobar pneumonia without empyema was therefore 12.7 per cent.

During the period, Oct. 18, 1917, to May 18, 1918, 2,956 cases of measles were treated in this hospital. The total number of measles pneumonia has been 181, making, for the period, an incidence of pneumonia in measles of 6.1 per cent. Of the 181 cases of measles pneumonia, 83 patients have died, a mortality of 45.8 per cent. Included among these 83 deaths, were 43 deaths from empyema. The mortality of measles pneumonia without empyema was therefore 32.5 per cent. There were, in addition, twenty-two instances of bronchopneumonia not included in the measles group. Among these there were no empyemas, but there were two deaths, a mortality of 9 per cent.

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1. The term "measles pneumonia" refers to pneumonia following measles. It was impossible, in many instances, to distinguish, clinically, lobar from bronchopneumonia, especially if empyema was an early complication.

Table 1 brings out the mortality incident to these different groups with reference to empyema.

TABLE 1.—Mortality with Reference to Empyema in Pneumonia

Lobar Pneumonia	Number	Number of Deaths	Mortality, Per Cent.
With empyema	142	87	61.2
Without empyema	526	67	12.7
Total	668	154	23.0
Measles Pneumonia			
With empyema	58	43	74.1
Without empyema	123	40	32.5
Total	181	83	45.8

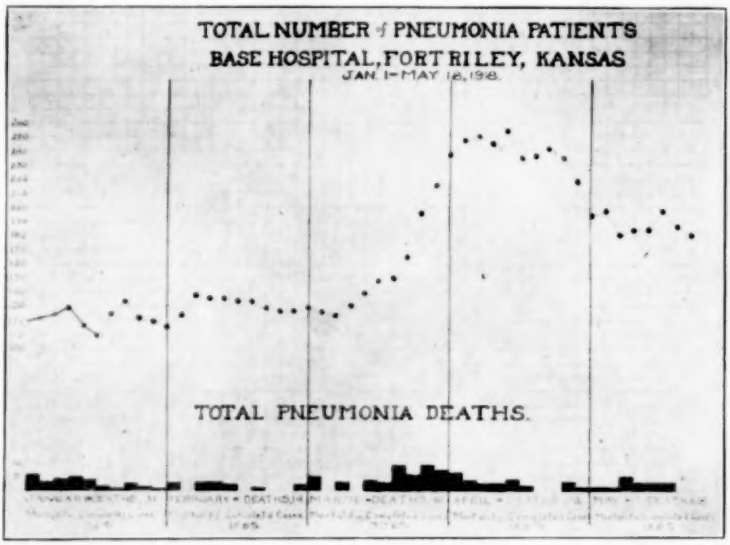

Fig. 1.—Graphic representation of total number of pneumonia patients at the Base Hospital, Fort Riley, Jan. 1 to May 18, 1918.

DISCUSSION

It will be seen that the mortality in lobar pneumonia was about half the mortality of the pneumonia following measles (23:45.8). It has been instructive to observe the varying mortality from month to month depending on features difficult to interpret except on the basis of differences in the virulence of the infection. Table 2 emphasizes this fact and shows how, irrespective of every facility for proper care, the mortality with the same general plan of treatment varied from month to month.

TABLE 2.—Variability of Mortality by Months

LOBAR PNEUMONIA

	Number of Completed Cases *	Number of Deaths	Mortality, Per Cent.
January	77	21	27.2
February	63	9	14.2
March	118	45	38.1
April	165	25	15.1
May	115	14	12.1

MEASLES PNEUMONIA

January	40	11	27.5
February	20	5	25.0
March	4	1	25.0
April	30	8	26.6
May	9	3	33.3

* The term "Completed Cases" is used to designate patients discharged from hospital either to duty or death.

Empyema was the most frequent and the most serious complication met with in lobar pneumonia as well as in measles pneumonia. This is shown in Table 3.

TABLE 3.—Empyema Incidence in Pneumonia

	Total Cases	Empyemas	Incidence, Per Cent.
Lobar pneumonia	668	142	21.2
Measles pneumonia	181	58	32.0
Bronchopneumonia	22	0	0
Total	871	200	22.9

PER CENT. OF EMPYEMA DEATHS TO TOTAL DEATHS

	Total Deaths	Empyema Deaths	Per Cent.
Lobar pneumonia	154	87	56.5
Measles pneumonia	83	43	51.6
Bronchopneumonia (not measles)	2	0	0
Total	239	130	54.3

That the fatality of this complication (empyema) varies likewise from month to month under the same general plan of treatment is shown in Table 4.

TABLE 4.—Fatality of Empyema by Months

LOBAR PNEUMONIA

	Completed Empyemas *	Deaths	Mortality, Per Cent.
February	8	3	37.5
March	34	29	85.3
April	22	14	63.6
May	33	7	21.2

MEASLES PNEUMONIA

February	5	4	80.0
March	2	0	0
April	13	4	30.7
May	4	2	50.0

* Many of these patients were admitted in earlier months but did not figure as completed cases until the month specified.

It will be noticed from Table 4 that the highest mortality in which empyema was the prominent associated pathologic condition occurred during the months of March and April. These were largely instances of overwhelming infection of rapid onset and death within a few days. The type of infection and the associated pathologic condition will be discussed under pathology.

CLINICAL DIAGNOSIS

It will not be necessary to lay stress on the varying clinical features of lobar pneumonia. The rapid onset of chill, fever and cough with tubular breathing and signs of consolidation, however small, sufficed, in the vast majority of cases, to establish the diagnosis. Abortive cases were occasionally seen in which, after twenty-four hours, all signs of tubular breathing and consolidation had disappeared. These were not included in the statistics.

The roentgenogram may be of great help in making a diagnosis of questionable consolidation. The patient, shortly after admission, should have a chest plate taken. Roentgenograms have been taken of the chests of patients in about 250 completed pneumonia cases. Consolidation may not infrequently be detected by this means before definite physical signs warrant a positive diagnosis. Such a plate serves the purpose of comparison with plates subsequently taken in the diagnosis of complications.

In the diagnosis of bronchopneumonia some dependence should be placed on the history of previous bronchitis or measles. The signs of bilateral involvement without definite areas of consolidation and the presence of moist crackling râles, especially during inspiration, were usually sufficient to establish the diagnosis. Unilateral bronchopneumonia was not infrequently observed. In bronchopneumonia the dyspnea was usually more marked, the accessory muscles were used in inspiration, cyanosis in many instances was a prominent feature, the sputum of a particularly ropy character, and the patient presented the picture so well described in the older term of "suffocative catarrh."

In the diagnosis of complications (Fig. 2) the aspirating needle was used early for the detection of empyema. Increased frequency in respirations or pulse rate, the presence of cyanosis, so-called "delayed resolution," a decreased fever but with increased pulse rate, should be sufficient reason for suspicion of this common complication.

Pus was frequently found without any increase in the temperature. The rule was that if either the temperature, pulse or respirations remained elevated, search was to be made for physical signs of fluid in the chest. Seldom were all the physical signs of fluid present, but if any one sign was present, paracentesis was justified. Skoda's resonance was present in large effusions. Weakened breath sounds,

diminished tactile fremitus with decrease in vocal or whispered voice resonance were the most valuable signs. Bronchophony was noticed in some instances or the voice sounds possessed the peculiar nasal twang described by Laennec as egophony. The roentgen ray was of little help in small accumulations of fluid, but was of great help in outlining larger accumulations associated with fibrinoplastic pleural thickening.

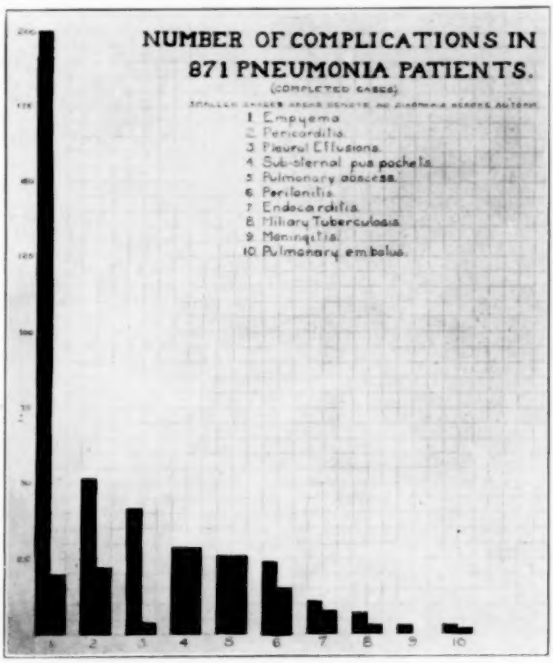

Fig. 2.—Complications in 871 pneumonia patients.

In performing pleural puncture it has been found beneficial to remember that the diaphragm may be higher on the affected side than is commonly believed, due to abdominal distention. The point usually selected was over the area of greatest dulness, after outlining the upper limit of the liver in front and side if puncture was to be done on the right side. Behind, below the angle of the scapula, or laterally in the post or midaxillary lines were the usual locations for puncture. In accumulations in front the nearer the puncture to the sternum the greater the danger because of the internal mammary artery and the larger vessels.

The leukocyte count was not of great value in the detection of complications, as will be seen from Table 5. It will be noticed that the average counts were higher in bronchopneumonia than in lobar pneumonia.

TABLE 5.—The Leukocyte Count in Pneumonia

	Uncomplicated Cases	Complicated Cases
Lobar pneumonia	64	28
Average count	14,960	16,100
Bronchopneumonia	10	7
Average count	20,450	19,650

Pericardial effusion was suspected when any diminution in the clearness of the heart tones became evident, particularly if this had been associated with an earlier definite friction rub synchronous with the heart beat. If signs of fluid, as evidenced by an increase in heart dulness, were apparent, paracentesis of the pericardial sac was done, in no instance with apparent damage. The point selected was usually slightly below and outside the nipple, the needle pointing upward toward the inner third of the left clavicle and backward. In one instance over 1,000 c.c. of fluid were removed in three aspirations. As will be observed in Table 6, serofibrinous or purulent pericarditis was found at necropsy in 51 instances, of which 22 were not diagnosed prior to death. Many of these showed friction sounds at some time during the course of the disease which could not be differentiated from a pleuropericardial friction rub, especially when associated with hyperpnea and rapid pulse. Pericarditis occurs frequently enough in pneumonia to make it an imperative rule to examine the heart with care at each visit. Serofibrinous pericarditis occurred clinically in approximately 4 per cent. of lobar pneumonias, in 2.2 per cent. of measles pneumonias. There were 31 instances. Twenty-four of the patients died. Pericarditis purulenta occurred only in association with empyema of subcostosternal pus pockets. Of this complication there were 20 instances, in all of which death occurred. At necropsy the pericardium was found distended with quantities of purulent fluid varying in amounts from 500 to 1,000 c.c. In patients coming to necropsy at a later stage the visceral layer of the pericardium and myocardium was covered with thick organized exudate producing the picture of the "shaggy heart." In one instance erosion of the muscle of the left ventricle had occurred, with fibrous thickening in the region of the A-V bundle, which had produced auricular fibrillation and a marked pulse deficit before death. The pus showed long chains of streptococci.

Diphtheria was simulated in two instances by edema of the glottis incidental to a streptococcic infection. The larynx should be examined

by means of a laryngeal speculum in any questionable case of beginning stridor, since the Klebs-Löffler bacillus is not an infrequent visitor to pneumonia wards.

Acute peritonitis was diagnosed in five moribund patients in whom the condition was not found at necropsy. Ascites was mistaken for peritonitis in one instance. These conditions were simulated by abdominal distention due to toxemic ileus. This tympanitic distention so frequently seen in pneumonia has been believed to be similar in nature to the so-called "paralytic ileus" following abdominal operation. That it is due to toxemia in pneumonia we have little doubt. In a number of necropsies on patients in whom this had been a prominent symptom there were found localized areas of the descending colon, 4 or 5 inches long, involved in spastic contracture. These areas involved the sigmoid and splenic flexure of the colon particularly. There were usually not more than two such areas involved. The colon above these areas of contracture was enormously distended with gas while the contracted areas were empty. The condition then resembles a spastic rather than a paralytic ileus. It deserves further study because of the divergent methods of treatment required properly to relieve the condition. This will be discussed under treatment. Peritonitis occurred only in connection with empyema. The extension was through the diaphragm on the side subjacent to the empyema. The abdominal surface of the diaphragm in these instances was covered with fibrinopurulent plaques of exudate. At a later stage general diffuse peritonitis was present.

As will be noticed in Table 7, showing the failures to diagnose the various complications, endocarditis was not diagnosed in 72 per cent. In a number of instances the endocardial lesions were slight, but were sufficient to attract attention at necropsy. In many instances (exact number not recorded), the heart dulness was observed to be increased to the right during the course of the disease. At necropsy the right side of the heart was found to be distended and apparently dilated, while the left ventricle was found to be firmly contracted in systole, probably as a result of the influence of digitalis administered to physiologic effect. This will be discussed under treatment. In one instance an open foramen ovale was found undiagnosed until necropsy in a patient with a typical "shaggy heart," the entire pericardium being filled with organized fibrinoplastic exudate.

It will be noted in Table 6 that subcostosternal pus pockets were found in 29 instances in 153 necropsies, and that the diagnosis was not possible prior to death in any case, although the presence of such purulent accumulations were suspected in many instances from the combination of clinical and roentgen-ray evidence. An explanation of the presence of these pockets in this location is offered in the descrip-

tion of the accompanying drawing (Fig. 3). This pocket of pus, which is usually situated on the side of the affected lung, but which may be bilateral, lies immediately beneath the sternum. It occupies the space between the median flap of lung composing the upper lobe as it lies above the fibrous layer of the pericardium. It is not in the mediastinum and should not therefore be called a mediastinal abscess.

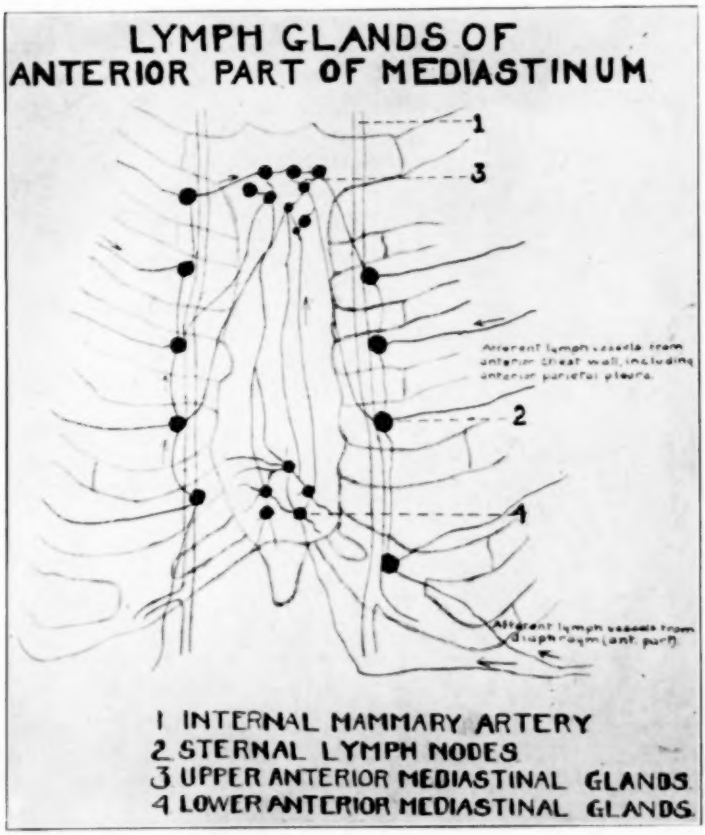

Fig. 3.—Diagrammatic representation of the lymph glands anterior to the mediastinum indicating possible location of pus pockets.

The term subcostosternal pocket describes the location and its boundaries. The pocket may communicate with other septal pockets or other portions of the pleura of the affected side. The vessels of the hilum may be its deepest limit or the opening to the pleura may occur through the normal pulmonary septa. This pocket is almost impossible

to drain laterally, anteriorly or posteriorly by the usual thoracotomy or costatectomy. This pocket may be primarily affected and all other portions of the pleura be apparently free from pus while this one alone remains undrained and unhealed.

TABLE 6.—The Ten Most Common Complications in Pneumonia Based on 871 Completed Cases (153 Necropsies), Base Hospital, Fort Riley, Kan.

	Number	Incidence, Per Cent.	Not Diagnosed Before Necropsy, Per Cent.
1. Empyema	200	23.0	10.0
2. Pericarditis	51	5.9	43.0
3 Large pleural effusions	42	4.8	9.5
4. Subcostosternal pus pockets	29	3.3	100.0
5. Pulmonary abscesses	26	3.0	100.0
6. Peritonitis	24	2.7	62.5
7. Endocarditis	11	1.2	72.0
8. Miliary tuberculosis	7	0.8	43.0
9. Meningitis	3	0.3	0.0
10. Pulmonary embolism	2	0.2	50.0

Thirty-three per cent. of pneumonia patients develop one or more complications.

This table does not take into account such readily diagnosed complications as otitis media or arthritis.

TABLE 7.—Probability of the Correct Diagnosis of the Complications of Pneumonia Founded on 153 Necropsies

	Found in, Per Cent.
1. Large pleural effusions	90.5
2. Empyema	90.0
3. Pericarditis (serofibrinous and purulent)	57.0
4. Miliary tuberculosis	57.0
5. Pulmonary embolism *	50.0
6. Peritonitis (subdiaphragmatic or diffuse)	37.5
7. Endocarditis	28.0
8. Subcostosternal pus pockets	0.0
9. Multiple pulmonary abscesses	0.0

* Two instances only.

If the infection traveled by way of lymphatic vessels from the lymph spaces in the alveoli of the lung and perivascular and peribronchial lymphatics it would reach the middle mediastinal lymph glands just below the bifurcation of the trachea, from which it would communicate to visceral nodes in the anterior and posterior mediastinal spaces and would produce a mediastinal abscess. We believe that the course of the infection is parietal rather than visceral, that it follows the lymph channels to the pleura from which afferent lymph vessels, draining the anterior chest wall including the anterior parietal pleura, lead to sternal lymph nodes of which there are usually six on each side along the course of the internal mammary arteries. The pus pockets occur in close proximity to these nodes due undoubtedly to breaking down of these glandular structures. They have constituted a unique and very serious complication.

So-called toxic arthritis occurred in ten instances of empyema. But one patient developed a suppurative arthritis in association with empyema in this series.

Blood cultures were taken from 100 patients with pneumonia, or suspected pneumonia, on admission. In one instance a hemolytic streptococcus was obtained from a patient with bronchopneumonia whose sputum also contained the same organism. In five instances a

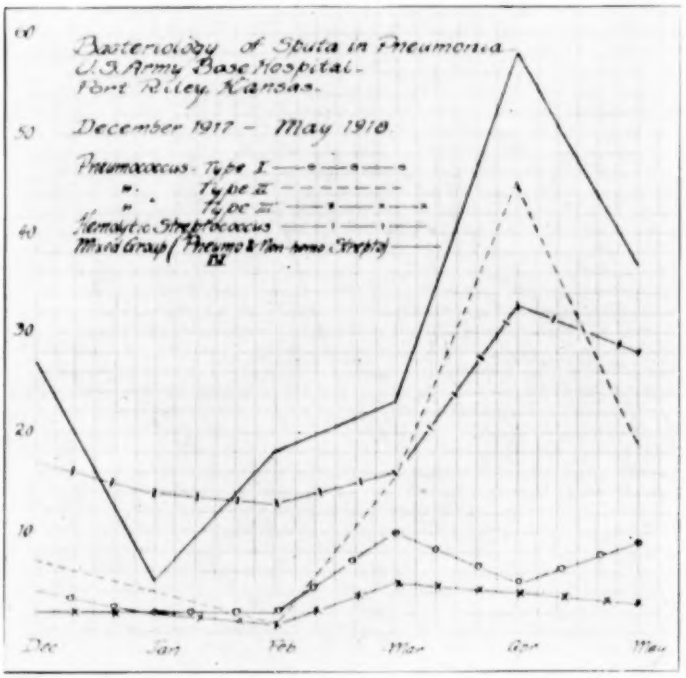

Fig. 4.—Curves representing the incidence of the different types of bacteria in the sputa in pneumonia.

pneumococcus was obtained, in two of which the patients did not develop pneumonia. The cultures were sterile in 94 per cent. Blood cultures have not therefore been of much assistance in this study of pneumonia. We have been impressed with the infrequency of ulcerative endocarditis, of phlebitis, of splenic or kidney infarcts or of meningitis as contrasted with the frequency of empyema, pericarditis and peritonitis in this study. This indicated spread by way of the lymphatics rather than by the blood stream.

TYPES OF INFECTION IN PNEUMONIA

During the interval, December, 1917, to May, 1918, sputum determinations as to type of infection were made in the hospital laboratory[2] in 428 completed cases of pneumonia.

TABLE 8.—Bacteriology of Sputa in Completed Pneumonia Cases

	Dec.	Jan.	Feb.	Mar.	Apr.	May	Total	Per Cent.
Pneumococcus Type I.....	4	2	2	10	5	9	32	7.7
Pneumococcus Type II.....	7	4	1	16	43	19	90	21.0
Pneumococcus Type III.....	2	2	1	5	4	3	17	3.9
Hemolytic streptococcus.....	17	14	13	16	33	28	121	28.2
Mixed Group (Pneumo. IV and Nonhemolytic streptococcus)	27	5	18	23	58	37	168	39.2
Total	..	..	..	..	..	..	428	

In 155 empyema fluids the hemolytic streptococcus was found in 106, or 68.4 per cent., the nonhemolytic streptococcus in 9, or 5.8 per cent. Table 9 shows the relation of streptococcus infection in the empyemas of lobar and measles-pneumonia.

TABLE 9.—Bacteriology of 155 Completed Empyemas

	Lobar Pneumonia	Measles Pneumonia	Total	Per Cent.
Pneumococcus	32	8	40	25.8
Streptococcus, hemolytic.....	75	31	106	68.4
Streptococcus, nonhemolytic.....	2	7	9	5.8
Total	109	46	155	

Table 10 brings out the mortality of the types of infection in 155 instances of completed empyema. It will be seen that the mortality in empyema, due to the streptococcus, was 61.7 per cent., while in empyema, due to the pneumococcus, the mortality was 45 per cent.

TABLE 10.—Mortality of Empyema as to Type of Infection

	Streptococcus			Pneumococcus		
	Total	Deaths	Per Cent.	Total	Deaths	Per Cent.
Lobar pneumonia.....	77	45	58.4	32	11	34.3
Measles pneumonia.....	38	26	68.4	8	7	87.5
Total	115	71	61.7	40	18	45.0

2. The method followed was that of the Rockefeller Institute mouse injection until Jan. 10, 1918, since when Avery's synthetic medium has been used. Until about March 15, 1918, a gram stain, a subculture in plain broth and on blood agar plate was made from the Avery medium culture. Since that date the subculture in broth has been discontinued. The precipitin method was used for a long period, but the agglutination method was found to be preferable and compulsory, of course, when bile was not available. In the differentiation of pneumococcus Type IV from the streptococcus, the bile test and the cultural characteristics on the blood agar plate were used.

DISCUSSION

The hemolytic streptococcus and the mixed group, pneumococcus Type IV and nonhemolytic streptococcus, were the organisms found in the sputum in 67.4 per cent. of 428 instances of completed pneumonia cases in this hospital. The streptococcus was the organism found in 74.2 per cent. of 155 instances of empyema. In January it

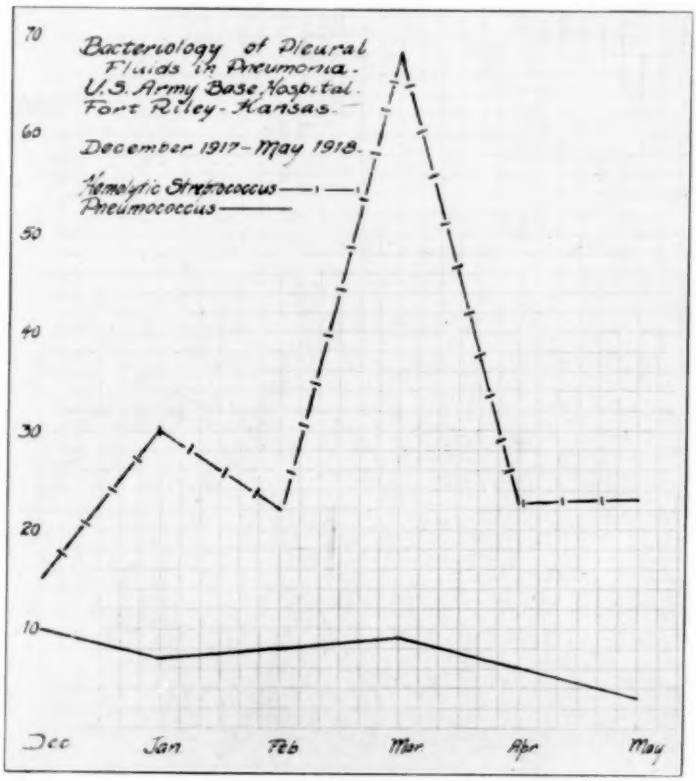

Fig. 5.—Curves showing the incidence of types of bacteria in pleural fluids in pneumonia.

was noticed, in a study of the sputum curve in the laboratory, for all sputa sent in, that Type II pneumococcus, including the atypical Type II, began to parallel the curve of the Type IV pneumococcus. In March the apexes of the curves for these types and the hemolytic streptococcus reached their height. It was during March that an influx of severe lobar pneumonia with frequent empyemas occurred.

The rapid occurrence, in these cases, of empyema, due to hemolytic streptococci, with rapid reaccumulation of fluid despite daily aspirations of quantities varying from 500 to 1,800 c.c., with death within a week and at necropsy a collapsed lung on the affected side, led us to believe that a combination or double infection had occurred. This condition was responsible for the greatly increased death rate in March and occurred in epidemic form (Figs. 4 and 5).

Since Type II pneumococcus is not strictly a "fixed" type and the Type IV pneumococcus is not "fixed" at all, it appears that an associationship exists between these groups and the hemolytic streptococcus, and that a closer study of the relationship of the hemolytic streptococcus to Types II and IV pneumococcus is highly desirable. Very few of the infections have been due to the nonhemolytic streptococcus.

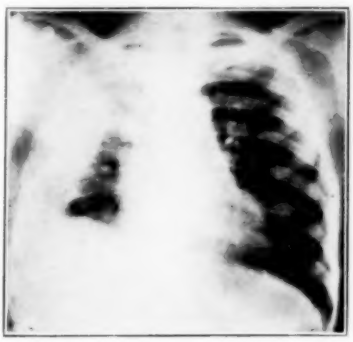

Fig. 6.—Diagnosis, walled off fluid, right side. After four aspirations of decreasing quantities of pus the patient recovered without operation.

It has been noteworthy that so many hemolytic streptococcic empyemas have occurred in pneumonia patients, in which pneumococcus Type IV was reported in the sputum — 22 of 72 instances, or 30 per cent. Bile solubility tests were not made in all of these instances, but the inference may be made that the pneumococcus, Type IV, predisposed to infection with the hemolytic streptococcus as a secondary invader. On the other hand, in 45 of 72 instances (62.5 per cent.) of streptococcic empyema, the sputum examination revealed streptococci. In other words, 92.5 per cent. of 72 streptococcic empyemas had either streptococcus or pneumococcus, Type IV, in the sputum. In 40 pneumococcus empyemas the sputum showed hemolytic streptococci in 5, nonhemolytic streptococci in 1, and pneumococcus, Type IV, in 15. In other words, 52.5 per cent. of 40 pneumococcus empyemas had either streptococcus or pneumococcus, Type IV, in the sputum.

Throat cultures were taken of lobar pneumonia patients several days after admission in fifty-nine instances. Thirty of these, or 50 per cent., showed hemolytic streptococci. An order was issued at this time requiring that all milk be boiled before use and prohibiting the use of uncooked cheese. Since that time throat cultures were made in eighty-one instances of lobar pneumonia on admission to the wards. It was found that 17 per cent. of these patients had hemolytic streptococci on admission. This number did not show an increase for cultures taken five and six days later. Data on throat cultures of measles patients, on admission and subsequently, are too incomplete for publication at this time.

Fig. 7.—Diagnosis, pericardial effusion. Recovered after aspiration.

PATHOLOGY

The basis of study in this series is founded on 153 necropsies, of which 107 (70 per cent.) were instances of lobar pneumonia and 46 (30 per cent.) were measles pneumonia. Included among the instances of measles pneumonia were 19 cases of lobar (41 per cent.) and 25 cases of bronchopneumonia (54 per cent.).

Particular interest is attached to the consideration of pneumonia following measles. In the early stage of lobular or bronchopneumonia the lungs were congested, edematous and crepitant, although on cut section little air could be expressed. Depending on the extent of lobular consolidation, light areas alternated with darker areas of infiltration, which darker areas corresponded on the pleural surface to blue-gray areas of collapse. The appearance was that of extensive lobular consolidation through the confluence of which more extensive involvement of portions of lobes occurred. Between these areas of lobular consolidation were noncollapsed air-containing portions, although these were much less prominent in number and appearance than the darker consolidated areas. Hemolytic streptococci were obtained in many instances from the lungs at necropsy.

Cole and MacCallum[3] have recently called attention to the interstitial type of pneumonia observed by them at the base hospital, Fort Sam Houston, Texas. The interstitial type in their cases was common after measles and was due to the streptococcus. On cut section the lungs showed prominent gray solid peribronchial nodules, with a shotlike feel to the fingers, due to edema, hemorrhages, organization and induration. Fibrinous plugs were found in the alveoli, while the alveolar walls were infiltrated with mononuclear cells. Few streptococci were found in the lungs, but large numbers were found in the pleural exudate. These streptococci were believed to be of low virulence, evidenced by abscence of spread throughout the body.

Fig. 8.—Diagnosis, purulent pericarditis; adhesive mediastinitis.

MacCallum found that lobular pneumonia also followed measles, due to an overwhelming streptococcus infection. In this type, patchy hemorrhagic areas of consolidation were present, containing large numbers of streptococci. The alveoli contained an exudation of polymorphonuclear cells and often was associated with necrotic areas in the lungs.

It is undoubtedly true that pneumonia of the interstitial type frequently follows measles. We have seen many such instances, but we have likewise frequently encountered this type of involvement not associated with measles. We believe that in these streptococcic pneumonias the difference between the interstitial and the lobular types is one of degree rather than kind. The interstitial type with partially plugged bronchioles and peribronchiolitis leading to small nodular

3. Cole, Rufus, and MacCallum, W. G.: Jour. Amer. Med. Assn., 1918, **70**, 1146.

consolidations occupying portions of a lobule, may at a later stage, due to confluence of such areas, involve neighboring bronchioles and present the picture of an extensive lobular pneumonia. Different stages of the process have been frequently seen to occur in the same lung. Microscopically,[4] in the interstitial type, the bronchioles were filled with leukocytes to the point of occlusion. The tissue surrounding the cut bronchiole was infiltrated with mononuclear cells. The walls of neighboring alveoli contained fewer mononuclear cells, polymorphonuclear cells and connective tissue cells with spindle-shaped nuclei. In the alveoli were many red blood cells and polymorphonuclear cells. In the more extensively consolidated portions of the

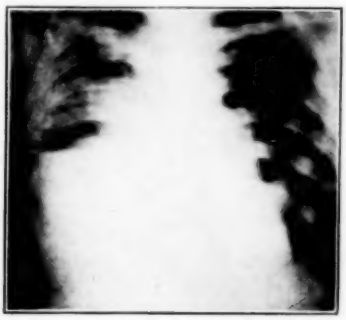

Fig. 9.—Diagnosis, free fluid, right side; upright position.

same lung, due to confluence of lobules, large mononuclear (wandering tissue) cells were found with many leukocytes and red blood cells.

In this series, the incidence of extension to serous membranes in lobar and bronchopneumonia shows but little difference (Table 11).

TABLE 11.—Necropsy Incidence

	Lobar Pneumonia,* Per Cent.	Bronchopneumonia, Per Cent.
Empyema	23.4	24.0
Peritonitis	3.0	2.8
Purulent pericarditis	2.5	1.7
Subcostosternal pus pockets	3.4	3.3

* Including lobar pneumonia following measles.

The hemolytic streptococcus was the organism most commonly found in these extensive complications, whether in lobar pneumonia or measles pneumonia.

4. We are indebted to Prof. A. S. Warthin of the Department of Pathology, University of Michigan, for the preparation of microscopic specimens and photomicrographs.

Pulmonary embolus involving the left branch of the pulmonary artery, because it is the straight branch, occurred in two instances. In both, thrombosis had occurred in the hemorrhoidal and prostatic plexus, involving the right hypogastric vein and extending into the inferior vena cava, from which a detached portion of the thrombus had been carried to the right side of the heart. The right hypogastric vein passes under the right external iliac artery at the brim of the pelvis, which makes a thrombosis more apt to occur in this locality. On the left side, the vein parallels the artery.

Except for a series of twenty-six multiple pulmonary abscesses, which were more frequently met with during a rapidly progressive type of streptococcic infection in lobar pneumonia in March, pulmonary abscess was not a frequent complication. These occurred in

Fig. 10.—Diagnosis, thickening of interlobar pleura, right side. Small quantities of pus aspirated twice. Patient recovered without operation.

lobar pneumonia when a streptococcic infection had apparently been superimposed on the lobar pneumonia. In view of the great number of thoracenteses made in diagnosing empyema, and in the daily aspirations, the relative infrequency of pulmonary abscess leads us to discount the common belief that there is any appreciable amount of danger in performing pleural punctures, due to the possibility of lung puncture and subsequent abscess formation.

Miliary tuberculosis was found at necropsy in seven instances presenting the symptoms of bronchopneumonia. The diagnosis was made in three of these patients prior to death. One instance of syphilitic interstitial pneumonia of rapid progress simulating bronchopneumonia was not diagnosed prior to necropsy.

GENERAL PLAN OF TREATMENT

It was possible to have separate dressing and operating rooms in the separate buildings given over to the care of lobar pneumonia and measles pneumonia. These were of great service in securing protection from the contagion of measles in the lobar pneumonia patients. One ward in each pneumonia section was set aside as a receiving ward. In this ward the first examination was made and the diagnosis established. The specimen of sputum for determination of the type of pneumococcus in lobar pneumonia was collected, whenever possible, in this ward. In the measles pneumonia receiving ward a throat swab was made for streptococcus culture.[5] Measles streptococcus carriers are now segregated from nonstreptococcic measles patients. Fresh air wards were utilized in the open air treatment of all serious cases.

Fig. 11.—Diagnosis, lobar pneumonia, right upper lobe.

In the other pneumonia wards, each patient was given approximately 1,000 cubic feet of air space.

During the first forty-eight hours after admission it was the plan of the medical service in the base hospital, since Jan. 15, 1918, to digitalize all pneumonia patients. The tincture of digitalis was used. Each batch of digitalis tincture was standardized according to the cat method of Hatcher,[6] as amplified clinically by Eggleston.[7] The estimated amount necessary to secure effect, according to body weight, was administered in doses of 2 c.c. to 4 c.c. every four hours until the total dosage had been given. Its use in this manner to prevent cardiac

5. A throat swab for culture of streptococcus is made on all measles patients on admission.

6. Hatcher, Robert A., and Brody, J. G.: Am. Jour. Pharm., 1910, **82,** 360.

7. Eggleston, Cary: Archives Int. Med., 1915, **16,** 1. We are indebted to Dr. Cary Eggleston of Cornell Medical College, N. Y., for numerous standardizations of digitalis tincture.

failure has been beneficial. The average tincture which we have used was standardized to a dosage of 0.17 c.c. per pound of body weight of patient. If the patient had not within a week had any form of digitalis, the following average total dosage was used:

For 120 pounds body weight — 20 c.c. in divided doses.
For 130 pounds body weight — 22 c.c. in divided doses.
For 140 pounds body weight — 24 c.c. in divided doses.
For 150 pounds body weight — 26 c.c. in divided doses.
For 160 pounds body weight — 28 c.c. in divided doses.
For 170 pounds body weight — 30 c.c. in divided doses.

Patients rarely vomited from the effects of digitalis administered in this manner. If the dosage should be carried further, to affect the vomiting center in the medulla, vomiting may occur. In the hundreds

Fig. 12.—Diagnosis, lobar pneumonia of right upper and middle lobes.

of patients treated with digitalis at this hospital, vomiting occurred from the effects of the drug in not more than four or five instances. We have seen but one instance of partial heart block, of temporary duration, which could be attributed to it. In only one instance have we seen a considerable rise of blood pressure (to 190) following its administration. The general circulatory effects were beneficial in sustaining the heart in pneumonia for the stress placed on it during an acute illness of such severity.[8] For intravenous emergency digitalis therapy, after the patient had received his total dosage of the tincture as outlined, we depended, when obtainable, on digipuratum. Digitalone, two $\frac{1}{10}$-grain tablets dissolved in 15 to 30 minims of sterile water, was also used intravenously for similar purpose. For emergency use orally, we also used Nativelle's crystalline digitaline. In the

8. The tincture of digitalis was made from Allen's leaves with 75 per cent. alcohol instead of the 50 per cent. alcohol prescribed by the U. S. P.

following tabulation is shown the proportion of deaths not associated with sepsis, and which may be attributed to circulatory failure for the predigitalis period and the digitalis period.

	Per Cent.
Predigitalis Period, October 18 to January 15	
Deaths not associated with sepsis	25.8
In lobar pneumonia	17.1
In measles pneumonia	46.3
Digitalis Period, January 15 to May 18	
Deaths not associated with sepsis	11.8
In lobar pneumonia	11.2
In measles pneumonia	14.8

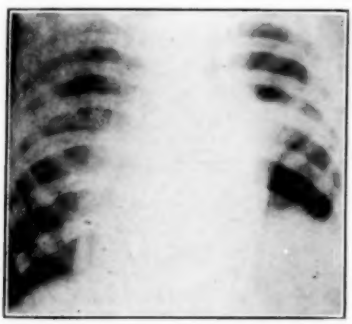

Fig. 13.—Diagnosis, left pyopneumothorax with adhesions to the parietal pleura. The patient died several days later with double empyema, multiple abscesses in left lung and endocarditis.

Pituitary extract was used on two indications — falling blood pressure and tympanitic abdominal distention. It was administered intravenously and intramuscularly. If the distention is due to paralytic ileus, pituitary extract may be of benefit because of its effect on involuntary muscle tissue in stimulating peristalsis. If, however, as mentioned, the distention is the result of spastic ileus, pituitary extract would be contra-indicated, and hot abdominal packs, a starch and opium enema, an opium and belladonna suppository, or a physiologic dose of atropin ($\frac{1}{75}$ to $\frac{1}{60}$ grain) should be used instead. Careless use of the rectal tube or frequent irritating enemas may produce thrombosis in the inferior and middle hemorrhoidal veins with extension to the hypogastric vein (right) leading to the possible occurrence of pulmonary embolism. Caffein and sodium benzoate or coffee was used as a general stimulant; morphin was used for restlessness. Veronal or trional was contraindicated. Atropin in doses of $\frac{1}{100}$ grain three times a day was of value in the treatment of pulmonary edema or bronchorrhea incident to bronchopneumonia.

SERUM THERAPY

Cole Type I serum was administered in doses of 100 c.c. intravenously after desensitization in Type I lobar pneumonias.[9] Its effect was, in a large percentage of cases, immediately beneficial. Within twelve to twenty-four hours the temperature would in some instances drop by crisis to normal. The dose was repeated daily for three or four days when indicated. There were thirty-two Type I pneumonias. Death occurred in five. One of these patients had pneumococcic otitis media and diffuse pneumococcic meningitis at necropsy; from one other patient meningococci and pneumococci were obtained by spinal puncture repeatedly before death from meningitis; while two more deaths were due to bilateral empyema. The mortality, including these four complications, was 15.6 per cent. Cole Type I serum was admin-

Fig. 14.—Diagnosis, left pyopneumothorax with adhesions to parietal pleura.

istered in twenty-seven of the thirty-two cases. Among those who received the serum there were four deaths (two had meningitis and one had bilateral empyema mentioned above). The mortality in the serum treated patients was therefore 14.8 per cent.

The autolyzed pneumococcic antigen of Rosenow was used in seventy patients with lobar pneumonia not due to Type I pneumococcus. Table 12 shows the day of the disease when the antigen was first administered, the number of empyemas and the mortality.

Among 219 completed instances of lobar pneumonia in which the patients were discharged during the same period and not treated with the antigen, the mortality was 14.6 per cent. In many instances fol-

9. Desensitization was carried out as follows: 0.5 c.c. subcutaneously followed in one hour by 1.0 c.c. subcutaneously. One hour later the serum was administered intravenously.

lowing the administration of the antigen the temperature fell abruptly by crisis after one or two doses. It is our belief, although no great differences in the mortality were affected by its use during the same

TABLE 12.—Completed Cases Lobar Pneumonia Treated with Autolyzed Pneumococcic Antigen[10]

Begun on	Number of Patients	Recoveries	Deaths	Empyemas *
1st day	22	14	4	4
2nd day	26	20	3	3
3d day	8	6	..	2
4th day	6	6	..	..
5th day	2	2	..	
6th day	2	1	..	1
7th day	1	..	1	..
8th day	2	..	1	1
10th day	1	1	..	..
Total	70	50	9*	11†

* Mortality 12.8 per cent. Incidence of empyema 15.7 per cent.
† Empyema patients still in hospital, May 18, 1918.

Fig. 15.—Diagnosis, right pneumothorax; left upper, resolving pneumonia. Following a severe attack of coughing the patient suddenly became extremely dyspneic and cyanotic and showed signs of a spontaneous, complete right pneumothorax, which was later confirmed by roentgenogram. There was gradual but complete recovery.

period when the antigen was not used in corresponding cases, that the duration of the disease was shortened. The results were gratifying in many instances. We shall continue its use. The dosage, 1 to 2 c.c. daily subcutaneously for four or five doses, produces practically no reaction. We believe, however, that the Cole Type I serum should be used in Type I cases.

10. Dr. Rosenow has kindly prepared for us an antigen containing a large fraction of our local strains of pneumococci which will be used in the treatment of pneumonia patients.

Through the kindness of Dr. Preston Kyes of the University of Chicago we were enabled to use his antipneumococcic chicken serum in thirty cases of lobar pneumonia due to the pneumococcus. One death occurred, a mortality of 3.3 per cent., with an empyema incidence of 13.3 per cent. During the corresponding period the mortality of lobar pneumonia in patients not treated with this serum was 14.2 per cent. The serum seemed to possess value in reducing the toxemia in pneumonia, but in a few instances, after desensitization, the intravenous administration produced severe reactions, with high temperature. These reactions have been entirely absent in recent batches of serum. Its value as a curative agent, judging from this small series of cases, is undetermined.

Fig. 16.—Brewer tube and Ewald bulb as used for suction drainage in empyema.

MEASLES PNEUMONIA

Measles patients received, since Feb. 15, 1918, a vaccine prepared from five local strains of streptococci and two strains of Pneumococcus IV, on the first, fourth and eighth days after admission. The incidence of measles pneumonia from October to February 15, prior to the use of the prophylactic vaccine, was 6 per cent. The incidence of measles pneumonia from February 15 to May 18 in 148 cases in which the prophylactic vaccine was used was 2 per cent. But one patient died of pneumonia in this latter series.

We have used antistreptococcus serum intravenously, after desensitization, in measles pneumonia due to the streptococcus with beneficial results in many instances. Agglutination tests of the local strains of streptococci encountered were made with stock serums, and it was found that agglutination occurred in dilutions of from 1 to 40 to 1 to 80 with a majority of the strains. The dosage was 50 c.c. intravenously, repeated daily for three or four doses.

THE TREATMENT OF EMPYEMA[11]

The total number of empyema complications following pneumonia in this series was 200. Of this number 119 men were operated on, all but a few of the earlier cases by Major Phillips; eighty-one men were not operated on. This latter group was made up of those patients who were not considered reasonable operative risks, or in whom the condition was not diagnosed prior to necropsy.

TABLE 13.—TYPE OF OPERATION FOR EMPYEMA

	Number	Mortality, Per Cent.
Rib resection	76	48.6
Thoracotomy	43	53.5
Right side	70	47.1
Left side	49	55.1

Fifty-nine per cent. of the empyemas occurred on the right side, 41 per cent. on the left side. Local anesthesia has been the method of choice, having been used in 85 per cent. of the operations.

TABLE 14.—ANESTHESIA IN EMPYEMA OPERATIONS

	Number	Mortality, Per Cent.
Local	102	50
General	17	53

If the plan is followed of early aspirations and late operations, mentioned later, the operation may be performed under ether anesthesia with comparatively little risk. We believe, however, that local anesthesia and nitrous oxid oxygen anesthesia are the methods of choice.

DISCUSSION

For the period October 18 to January 29, early operation was performed on all empyemas. During this period 83 patients were operated on, of whom 52 died, a mortality of 63.8 per cent. It has been possible, in Army hospitals, where the patients are under complete control from the beginning of their illnesses, to diagnose empyema earlier than has been possible in civil life. For the period mentioned in which early operation was performed the presence of pus containing organisms was considered to be a sufficient indication.

Beginning on January 12 the medical treatment of this condition was changed in several particulars as follows: As soon as the diagnosis of empyema was made during the course of pneumonia, aspiration,

11. May 18 there were under treatment 182 patients with pneumonia, among whom there were forty-six instances of empyema in which operation was performed.

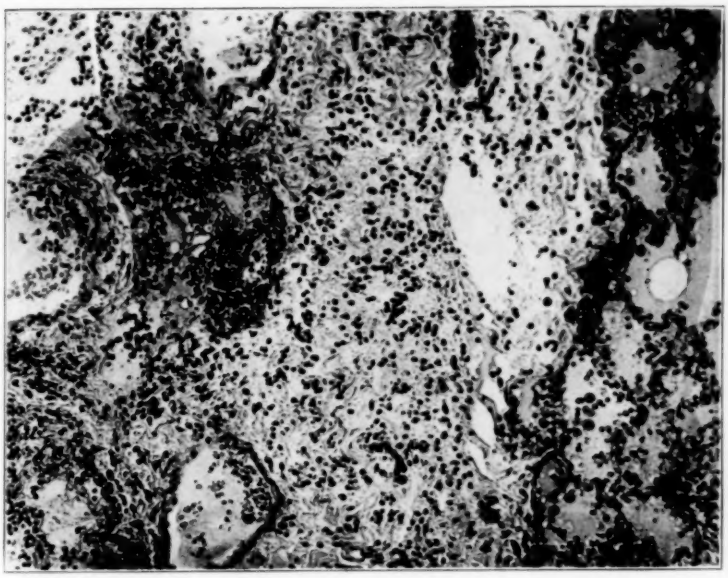

Fig. 17.—Bilateral streptococcus lobular pneumonia following measles. Early stage peribronchial infiltration; leukocytes in cut bronchioles; mononuclear cell infiltration in walls of alveoli.

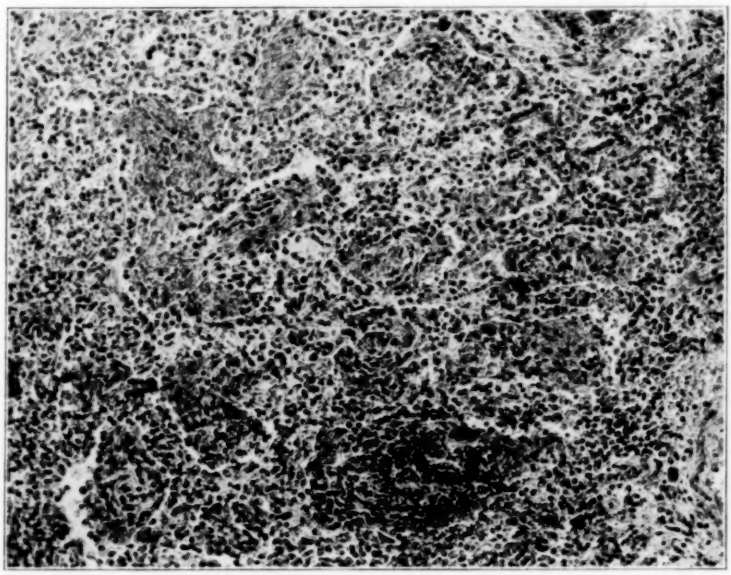

Fig. 18.—Bilateral streptococcus lobular pneumonia following measles. Occlusion of alveoli with plugs of fibrin and celluar debris.

using the Potain apparatus, was done, as a rule, every alternate day. This was continued until the pus became too thick for aspiration — for twelve to fifteen days. When the pneumonic process had subsided the advisability of operation was considered. If the pus became too thick for aspiration and it was not considered that the patient's condition warranted operation, intrapleural lavage was practiced at the time of aspiration, in closed circuit, by connecting a bottle containing warm saline solution to the aspirating tubing. In this manner thick

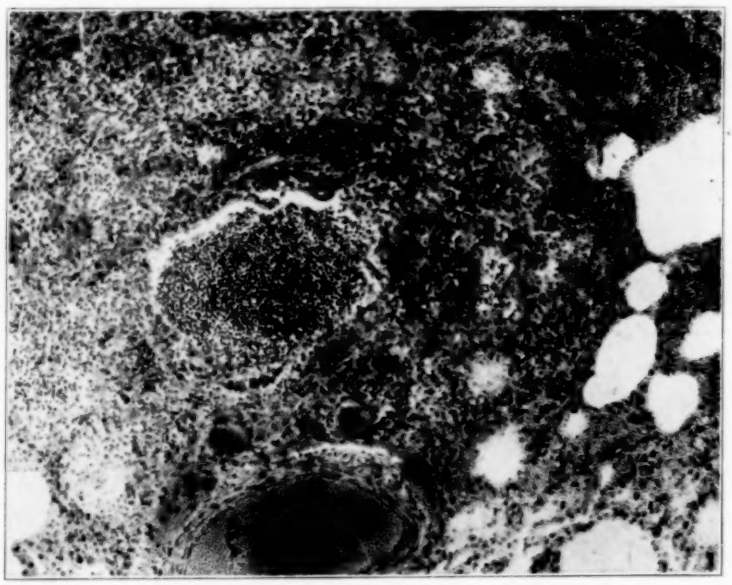

Fig. 19.—Bilateral streptococcus lobular pneumonia following measles; the cut bronchiole filled with leukocytes; the tissue surrounding shows mononuclear cell infiltration. The lungs showed air containing tissue in many areas.

pus could be diluted sufficiently to permit aspiration. Care was taken at the time of all aspirations, whether with the syringe or with the Potain apparatus, to prevent collapse of the lung by admission of air. The operation was not performed until twelve to twenty days had elapsed. The clinical judgment of two or three physicians, who followed the course of the infection from day to day, was utilized in deciding the best time for operation.

In all, eleven patients recovered by repeated aspirations without operation. The number of aspirations in these patients varied from one to ten. In one of these an aggregate of 835 c.c. of pus were removed by five aspirations; in another 7,660 c.c. of pus were removed

by eight aspirations, while in another 635 c.c. of pus were removed by ten aspirations. In five of the eleven the empyema was due to hemolytic streptococci; in one, to pneumococcus Type II; in one, to pneumococcus Type III, and in two, to pneumococcus Type IV. In one, the type of pneumococcus was not determined. Of these eleven empyemas, nine followed lobar pneumonia and two followed measles pneumonia.

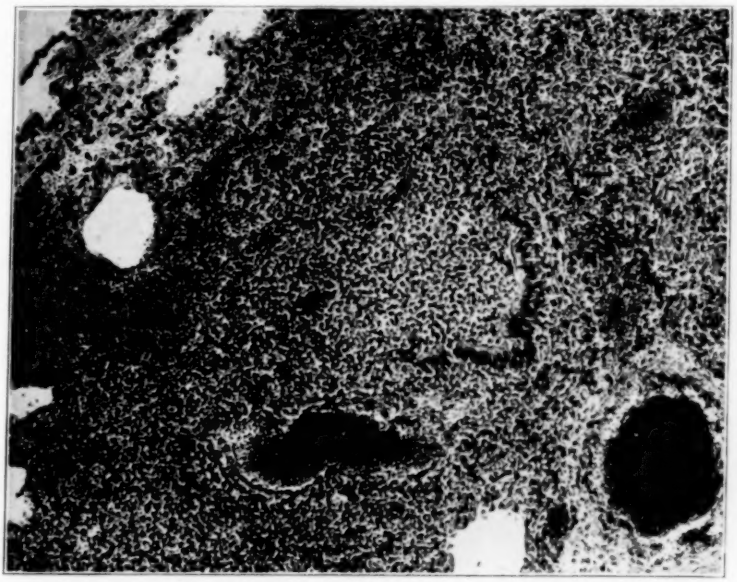

Fig. 20.—Bilateral streptococcus lobular pneumonia following measles with localized abscess formation.

At the time of operation the Brewer tube was preferred, to which was attached a partially collapsed Ewald bulb (Fig. 16). Negative pressure and suction were readily obtained in this manner. The tube was clamped and the bulb emptied whenever the patient complained of pain in the chest. In all of the earlier operations the ordinary rubber drainage tube was used and was latterly used when it seemed more suitable in order to reach a pocketed area of pus, such as an interlobar empyema. Since January 12 neutral solution of chlorinated soda (Dakin's solution) has been used for the daily irrigation of empyema wounds. There was a marked decrease in the odor and the amount of discharge was lessened in many instances. Operations were

begun, after preliminary aspirations as outlined, on January 29. The comparative results for the two periods are shown in Table 15.

TABLE 15.—Operative Mortality in 119 Completed Cases of Empyema

	Number	Deaths	Mortality, Per Cent.
Early operations not preceded by repeated aspirations (October 18 to January 29)	83	52	63.8
Late operations preceded by repeated aspirations (January 29 to May 18)	36	8	22.2

There were, on May 18, 46 operated empyema patients in the hospital, of whom 44 were classified under late operations. Of these 44 patients, the prognosis was considered favorable in 38 and unfavorable in 7. If these patients are added to the foregoing list of late operations, for purpose of comparison and to sustain our argument for the late operation the mortality will, according to present judgment, be expressed as shown in Table 16.[12]

TABLE 16.—Mortality After Late Empyema Operations

	Number	Deaths	Mortality, Per Cent.
Late operation preceded by repeated aspirations (January 29 to May 18)	80	15	18.7

These tables have been particularly interesting to us in view of the fact that the mortality of pneumonia with operated empyema, by this plan of treatment, has been reduced to a point not much higher than pneumonia without empyema.

TABLE 17.—Comparative Mortality in Empyema

	Number	Deaths	Mortality Per Cent.
Pneumonia with empyema, nonoperated	81	70	86.4
Pneumonia with empyema, early operation	83	52	63.8
Pneumonia with empyema, late operation	36	8	22.2
Pneumonia without empyema	671	109	16.2
Total	871	239	27.4

Sept. 25, 1918, the completed figures were as follows:

	Number	Deaths	Mortality, Per Cent.
Late operation preceded by repeated aspiration	80	13	16.2

On September 25 the completed figures for the early operation were as follows:

	Number	Deaths	Mortality, Per Cent.
Early operations *not* preceded by repeated aspirations	85	52	61.2

12. The mortality has been decreased since this table was completed in May.

For about two months the injection of stock antiserum (pneumococcic and streptococcic) in quantities of 75 to 100 c.c., was made intrapleurally after repeated aspirations. We could find no evidence that this was of decided benefit.

CONCLUSIONS

1. The mortality in pneumonia in this series of cases, observed over a period of seven months, varies from month to month with the type of infection.

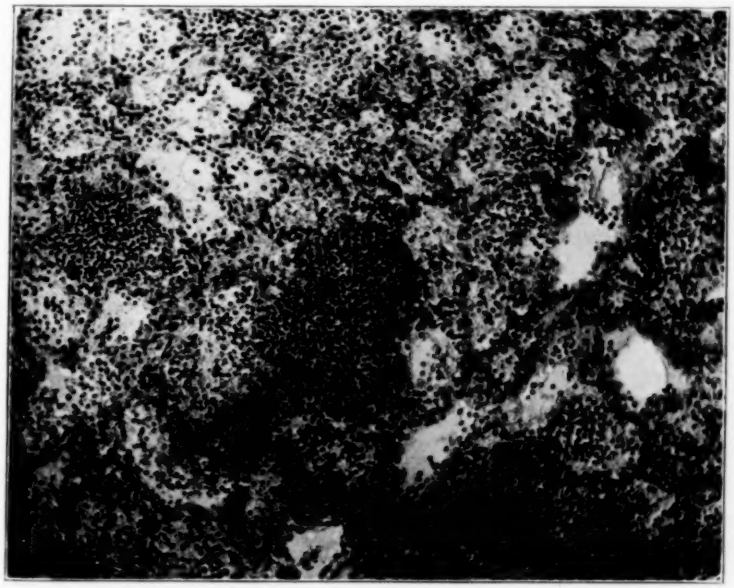

Fig. 21.—Bilateral streptococcus lobular pneumonia following measles. The patchy areas of consolidation are seen; many alveoli contain red blood cells and polymorphonuclear cells.

2. The mortality in measles pneumonia is approximately twice as high as lobar pneumonia. Interstitial pneumonia is believed pathologically to be an early stage of lobular bronchopneumonia. In both, streptococci were the predominating organisms. In the interstitial type death may occur before the process has extended sufficiently to produce extensive consolidation, through the confluence of lobules, and the condition be recognized pathologically as bronchopneumonia.

3. The use of a standardized tincture of digitalis, in sufficient dosage to produce physiologic effect, is believed to be responsible for

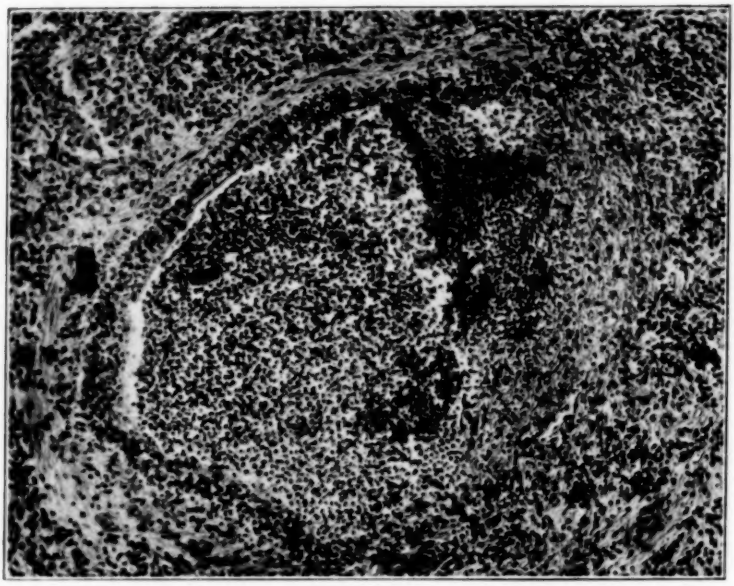

Fig. 22. — Bilateral streptococcus bronchopneumonia following measles. Bronchus filled with purulent exudate; beginning suppuration of wall.

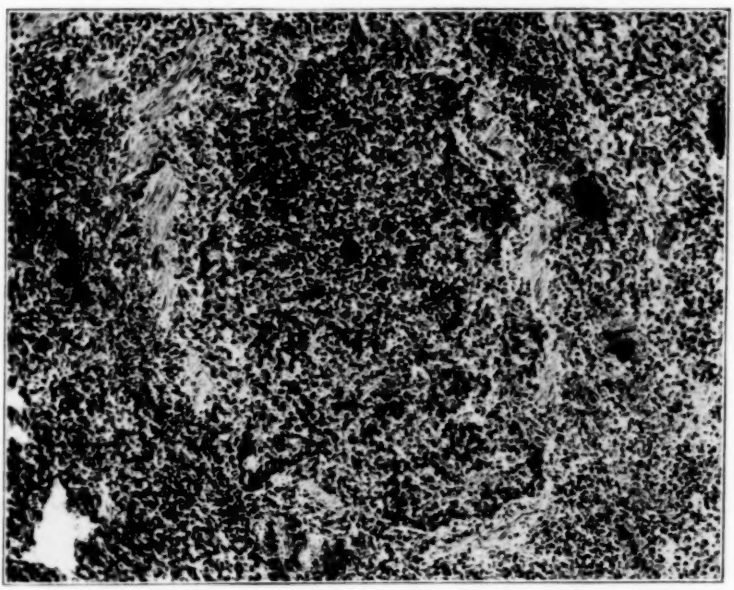

Fig. 23. — Bilateral streptococcus bronchopneumonia following measles. Bronchus with complete destruction of epithelium filled with pus in the middle of an atelectatic area.

a decrease of deaths in this series not associated with empyema or other septic complications; that is, the deaths which are associated with cardiac failure.

4. Empyema occurred in 23 per cent. of 871 instances of pneumonia and was responsible for 54.3 per cent. of the deaths.

5. Early diagnosis of empyema is essential. Repeated aspirations, as described in the foregoing, for from twelve to fifteen days, followed by late operation, has reduced the mortality from 61.2 per cent. to 16.2 per cent.[12]

6. The mortality of streptococcus empyema in relation to the mortality of pneumococcus empyema is approximately that of a ratio of 3 to 2.

7. Empyema patients should be retained in the medical service after operation. The surgeon assigned to the medical service for this work should spend his time in the pneumonia wards for this special duty. Complications such as extension of pneumonia to the opposite side, or reinfection of the affected lung, are recognized more promptly by the physicians of the medical service who have observed the patient from the outset.

8. The necropsies of this series have shown in many instances purulent accumulations beneath the sternum, which may be designated subcostosternal pus pockets. Infection apparently reaches this inaccessible location by way of the parietal lymphatics leading to substernal lymph nodes. The diagnosis of this condition can, as a rule, only be made at necropsy. Drainage of these pockets offers great difficulty. Extension to the pericardium frequently occurs in connection with these pus pockets.

9. The relationship of pneumococcus, Types II and IV, to hemolytic streptococci of high virulence deserves further study.

10. Cole Type I serum should be used in Type I lobar pneumonia. Rosenow's autolyzed pneumococcic antigen and Kyes' antiserum have been of apparent benefit in the treatment of lobar pneumonia.

11. A prophylactic vaccine administered to measles patients has appeared to possess some value, when administered on the first, fourth and eighth days after admission, in the prevention of pneumonia.

PNEUMONIA AND EMPYEMA AT CAMP SEVIER

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Recent rather numerous reports from the various army camps throughout the country concerning the incidence and causative agent of pneumonia, during the last winter, have mentioned frequent infection with *Streptococcus hemolyticus* and less frequent occurrence of pneumococcus infection. Reports from the different camps would indicate that the predominating organism is not the same in all localities. In Camps Funston, Dodge, Custer and Lee hemolytic streptococcus has been reported as the prevailing organism. At Camps Wheeler, Beauregard, Hancock, Jackson, Logan, Sheridan and Travis more pneumococcus infections are reported.

In the findings so far published attention has been directed chiefly to the study of bronchopneumonia and, more especially, empyema. There has been very little comparative study of lobar and bronchopneumonia. The studies of the commission headed by Cole and McCallum[1] at Fort Sam Houston, have been made with this point in view and their results would indicate that the true lobar pneumonia is now, as formerly, a pneumococcus infection, whereas the bronchopneumonia, or postmeasles pneumonia, is predominantly streptococcic. In certain other camps these postmeasles pneumonias and empyemas are reported as being frequently pneumococcic.

The present report has been undertaken in an attempt to present a comparative study of lobar pneumonia and bronchopneumonia as they have occurred at Camp Sevier and to draw conclusions regarding the type of infection and the complications that have arisen. Five hundred and sixty-seven cases of pneumonia were admitted to the base hospital prior to March 31, 1918. This group divides itself into 234 lobar pneumonia and 333 bronchopneumonia patients. Those cases which have occurred subsequent to March 31, during the preparation of this report, are not incorporated in the accompanying statistical review, but several showing unusual features have been included in the discussion.

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1. Cole, Rufus, and McCallum, W. G.: Pneumonia at a Base Hospital, Jour. Am. Med. Assn., 1918, **70,** 1146.

INCIDENCE

Of 9,650 admissions to the Base Hospital, 2.4 per cent. were for lobar pneumonia, and 3.4 per cent. for bronchopneumonia. In Chart 1 is shown the total number of lobar cases in the hospital on each day from Nov. 23, 1917, until May 1, 1918. During the latter part of December and during the months of January and February there was a high incidence of the disease, there being on February 3 as many as seventy-six cases. As shown by the weather notes in Chart 2 the steady increase during the month of January was during a period of very inclement weather and, following the onset of pleasant weather about February 6, there occurred on February 15 a decided fall in the curve which persisted throughout the remaining period. In April there were two other rises in the curve. The first followed by a few days a parade in which the soldiers had all become rain-soaked. At this time also a mild epidemic of influenza occurred which persisted for two or three weeks. The second rise in the April curve accompanied an increase in the influenza. These postinfluenzal pneumonias were chiefly lobar in type, although a few were bronchopneumonias, and they were all unusually sick. The incidence of empyema in this later series was also much higher than in the series up to March 31, being as high as 50 per cent.

In regard to the incidence of bronchopneumonia, this camp was comparatively free from disease during the month of September and the first weeks of October, 1917. With the influx of 8,000 draft men, there was then inaugurated a division wide epidemic of measles. Many of the new men coming from other camps had the measles rash on arrival, and others had only recently been in communities where the disease was endemic. As a result, 3,520 cases, or 12.8 per cent., of the entire strength developed in the division. One thousand and twenty-nine patients were in the base hospital at some time of their illness. Of the 333 cases of bronchopneumonia which soon developed, 292 were very definitely postmeasles.

In Chart 3 the morbidity curves of bronchopneumonia and measles show not only the correspondence between the two diseases, the bronchopneumonia lagging somewhat behind the measles, but the chart also shows, especially in the month of January, the absence of relationship between the bronchopneumonia incidence and that of lobar pneumonia as seen in Chart 1. As a discussion of the clinical records will show, lobar pneumonia was a complication of measles only in a small number of cases and was on the whole a primary affection. Chart 3 also indicates that with the onset of pleasant weather in February and at a time when more effectual quarantine and isolation were in effect in the camp and in the hospital, respectively, bronchopneumonia followed

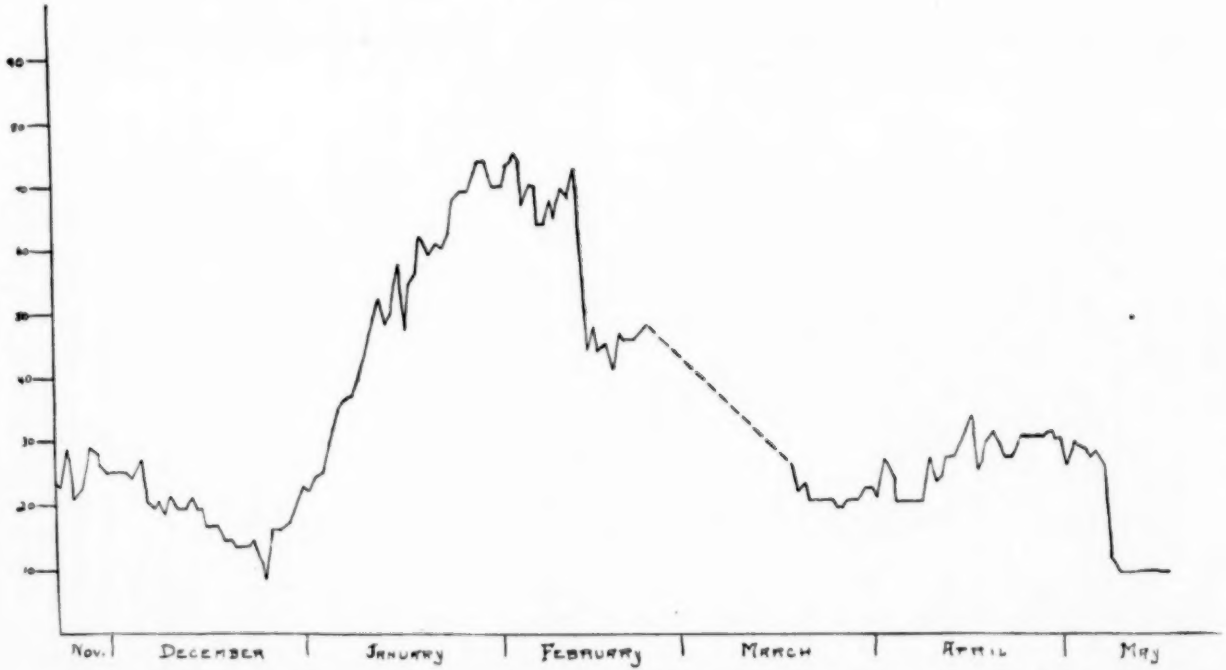

Chart 1.—Showing the number of lobar pneumonia cases in the hospital from Nov. 23, 1917, until May 1, 1918. The highest incidence of the disease occurred on February 3, when seventy-six patients were in the hospital.

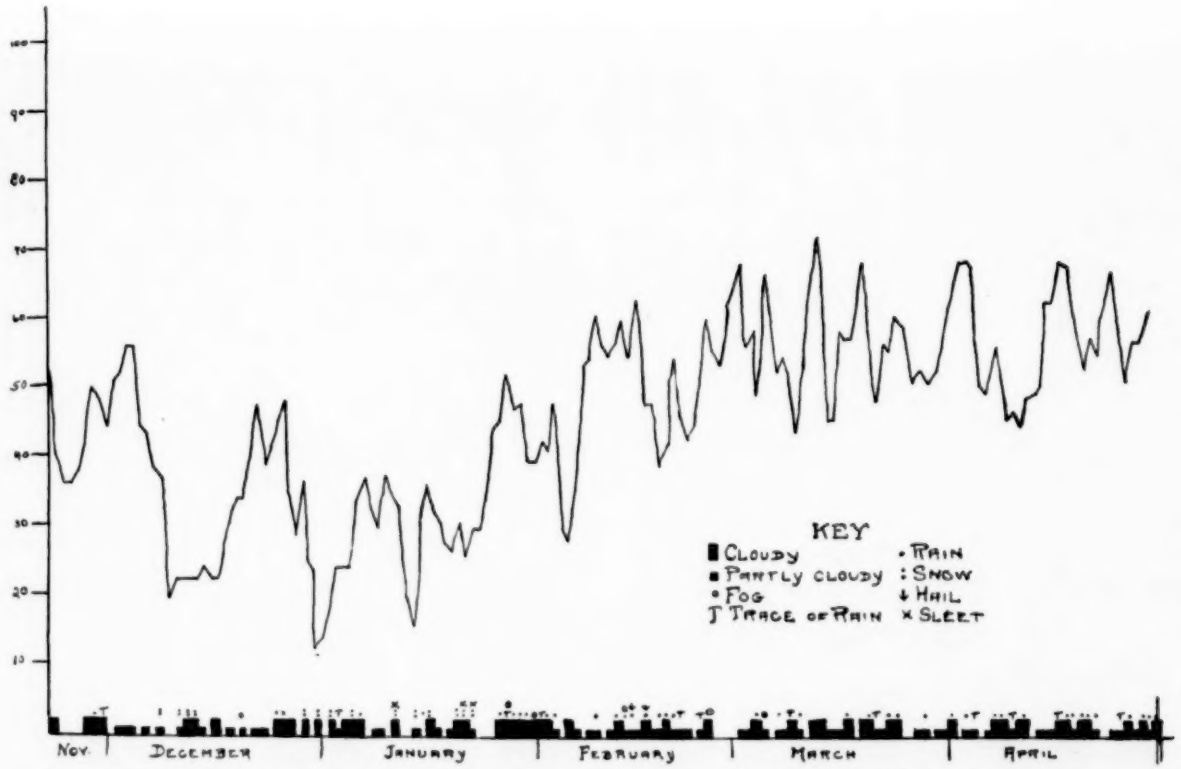

Chart 2.—Weather chart giving the temperature curves and data regarding the weather during the time the pneumonia cases described in this article occurred. As recorded by the chart there was a high incidence of the infection during the stormy periods.

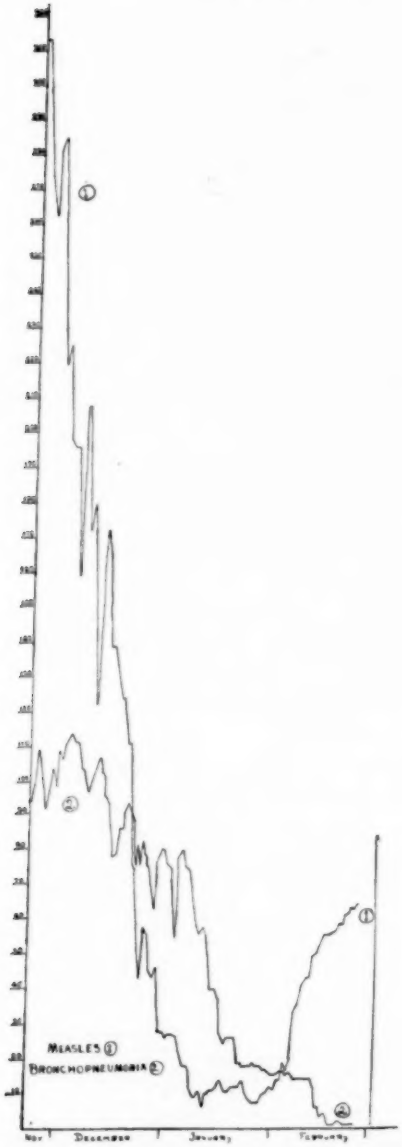

Chart 3.—Morbidity curves of the measles and bronchopneumonia cases which show the relationship between these diseases. The bronchopneumonia cases lagged somewhat behind the measles epidemic.

measles in a decidedly smaller number of cases than had been the case in November and December. Weather conditions probably played some rôle here, but the prevention of transmission of infection from one measles patient to another was undoubtedly of very great importance in securing the low morbidity during February.

Age.—The age variation of the patients under treatment was necessarily restricted to the age of soldiers in the army with the exception of a few older men such as officers, cooks and bakers. The youngest patient was 17 years old and the oldest 51. In both lobar pneumonia and bronchopneumonia the largest age frequency was 22 years. The greater number of patients were between 18 and 25 years of age.

Occupation.—The majority of the patients gave their occupation as farming. Of 157 farmers with lobar pneumonia twenty-nine, or 18.6 per cent., died. The average total mortality for the disease was 14.9 per cent. Of 265 farmers among the bronchopneumonia patients, ninety-four, or 35.4 per cent., died. The average mortality for this type of pneumonia was 36 per cent. Thus it is apparent that among farmers a fatal outcome was slightly more frequent in lobar pneumonia and equally as frequent in bronchopneumonia as the total respective mortalities. Farmers formed the majority of the latter class. Forty-four different occupations are represented.

ETIOLOGY

Lobar Pneumonia.—At the present time we understand two general causes of lobar pneumonia, the first, direct contagion, and the second, infection in individuals whose resistance has been temporarily lowered from exposure to wet or cold or from other causes. Infection with Types I, II or III pneumococci has been shown to result in a high percentage of cases from direct transmission. In the case of infection with Type IV pneumococcus which is found in the bacterial flora of the mouths of 50 to 80 per cent. of normal individuals, the possibility of contact infection is more problematic and more remote. The type of pneumococcus in the sputum has been determined by the Avery[2] method in 139 cases of lobar pneumonia. Ten per cent. of these have shown Type I organisms; 7.9 per cent. Type II, and the remainder, 82.1 per cent., have been of Group IV. There have been no Type III infections. These results would indicate that the disease as seen in this camp is chiefly a result of exposure among the soldiers to the rigors of outdoor life. The following observations appear to bear out this conclusion.

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2. Avery, O. T.: Determination of Types of Pneumococcus in Lobar Pneumonia, Jour. Am. Med. Assn., 1918, **70,** 17.

A SERIES OF FIFTY PATIENTS QUESTIONED AS TO POSSIBLE FACTORS IN THE CAUSATION OF THEIR PNEUMONIA

Each of fifty lobar pneumonia patients, admitted for the most part during the month of February, was asked the following series of questions:

1. Before you were taken sick were you wearing the khaki uniform or olive drab woolen?
2. Were you wearing winter or summer underwear?
3. How many blankets did you have on your cot? Comforters?
4. Were you warm enough at night?
5. Was your food satisfactory as to quality? As to quantity?
6. How many were sleeping in your tent?
7. Was it the regulation pyramidal tent? Otherwise how large was it?
8. Did it have a floor?
9. Had you a sore throat, cold, cough or "grippe" before you were taken ill this time?
10. What illness have you had recently?
11. Was anyone else in your tent sick recently? Colds? Cough? Pneumonia?
12. Did the men in the tent spit on the floor? On the stove? In the stove?
13. Had you recently been out in bad weather? Been on guard duty? Been wet?

The information obtained may be summarized as follows:

1. Thirteen, 26 per cent., did not have the woolen blouse. All had the wool breeches and winter overcoats.

2. All were supplied with winter underwear.

3 and 4. None admitted that bedding was insufficient, claiming to be warm and comfortable at night.

5. In practically every instance food was entirely satisfactory.

6. The regulation number of men in a pyramidal tent is five. In eleven instances there were six men in a tent, three times there were seven, four times there were eight, and only two men reported as many as nine soldiers sleeping in their tent. Twenty-two of the patients reported five men in their tent and four had but four men. Twenty out of forty-six men were, then, living in more or less crowded circumstances. This corresponds to the findings of Surgeon-General Gorgas during the building of the Panama Canal where the incidence of pneumonia fell remarkably when the laborers were removed from barracks into individual cabins.

7. All but four slept in the regulation tent.

8. Nearly all the tents had floors.

9 and 10. Sixty per cent. of the patients had had a preceding head cold, 4 per cent. had had influenza and 2 per cent. were suffering from acute follicular tonsillitis. Five cases, or 10 per cent., had had previous measles, but only in one instance did the pneumonia follow it immediately. Four per cent. had had mumps a short time previously.

11. In 32 per cent. nobody else in the tent was sick. In 26 per cent. both the patient and some of his tentmates were sick. In 8 per cent. the patient was well but one or more of his mates had a head cold. In one instance a tentmate had come down with pneumonia five days previously. In connection

with this it is well to refer to the report of Major Zinsser[3] from Camp Wheeler, in which he reviews a survey made on certain companies where the type of pneumococcus in the mouth was determined on every individual. He concludes that there is quite definite evidence of infection of tentmates by carriers and that company infection is probably of equal importance to tent infection.

12. Only six instances of promiscuous spitting were reported.

13. Fifty per cent. gave a definite history of exposure and 20 per cent. alone had been on guard duty a few days before.

One patient in this series was a hospital orderly who had been in good health and who came down with Type I pneumonia while attending a patient ill with that type of infection.

Bronchopneumonia.—Regarding bronchopneumonia it is interesting to note that of 333 patients, fifty-five gave a history of cough, cold or other respiratory tract infection previous to the onset of measles prodromata. Of 333 cases of uncomplicated measles, only fourteen gave a similar history. It would thus appear that preceding upper respiratory tract infection may be a factor in the development of postmeasles pneumonia. On the other hand, the mortality among those cases of bronchopneumonia giving such a previous history was slightly lower than the general bronchopneumonia mortality.

Previous Diseases.—It has been suggested by some that the fact that most of the soldiers had been farmers and had not had the usual infections of childhood, accounted in part for the high incidence and mortality from disease in camp; that they had not, through past diseases, had an opportunity to build up some degree of general immunity to infection. The subject of previous occupations has already been discussed. A summary of the incidence of all infectious diseases in the past histories of lobar pneumonia cases gives 561 infections. In other words, there was an average of 2.3 infectious diseases in the past history of each man. Among the bronchopneumonias the histories of infectious disease totalled 497, making 1.4 for each man. Among the bronchopneumonias 47.7 per cent. of the ninety patients giving entirely negative past histories died. This is higher than the general mortality of 36 per cent. The mortality among the ten cases of lobar pneumonia with negative histories was 20 per cent. as contrasted with a general mortality of 14.9 per cent. These findings would indicate that the foregoing supposition has some basis in fact, but for proof of the contention the results should be compared with results in other camps where the population was chiefly urban.

History of Recent Measles Infection.—Of the 333 cases of bronchopneumonia, 292 were secondary to measles, two each followed mumps and otitis media, one case occurred after cerebrospinal menin-

3. Duncan, Louis C.: An Epidemic of Measles and Pneumonia in the Thirty-First Division, Camp Wheeler, Ga., Mil. Surgeon, 1918, **42**, 123.

gitis and fourteen were preceded by influenzoid attacks. In the remaining twenty-two cases no relationship to prior disease was evident from the histories. Only thirty of the total postmeasles bronchopneumonias had been discharged to duty in the interval between the measles and pneumonia.

In the case of lobar pneumonia 148, or over one-half of the patients, had had remote measles infection. Of these, but five cases had been infected during their stay in camp. Cases with recent measles, that is under one month interval, numbered but thirty-one. Of these, six were admitted with the rash and the seventh developed it on the day following admission. The others had been convalescent for one week or longer. We were impressed, first, with the fact that postmeasles pneumonia was, as a rule, bronchopneumonic in type, and second, that whereas bronchopneumonia followed measles with no intervening period of good health, lobar pneumonia, when it did occur, usually following an interval of convalescence.

Incidence of Hookworm.—The stools of 159 patients were examined for parasites. Hookworm ova were found in 21.3 per cent. During this same period routine examinations of all admissions to the hospital gave over 20 per cent. of positive results. A divisional hookworm survey of 22,898 apparently healthy soldiers showed that 18.6 per cent. were found to harbor the parasite. All of these figures correspond quite well. On the other hand, among the bronchopneumonia patients 50 per cent. of those who had hookworm died, while only 17 per cent. of the negative ones proved fatal. Unfortunately, of the lobar pneumonia patients who died, only two had had hookworm examinations. These were negative. Seventy-three examinations were made on those who recovered, and of these fourteen were positive. Two of the latter passed through a severe illness, two had but a mild pneumonia and the ten remaining had a course of average severity.

History of Alcohol.—Among the lobar pneumonia patients alcohol was denied in 136 instances. Moderate use of intoxicants was admitted in eighty-one cases and an excess in seven. Of the members of the first class, 14.7 per cent. died; of the second, 17.3 per cent., and in the case of those who drank to excess 14.2 per cent. died. All of these mortality percentages correspond well with each other and with the general mortality of 14.9 per cent. In only one instance were there findings which might be interpreted as the results of excessive use of alcohol. Among the bronchopneumonia victims, seventy-nine patients admitted a moderate use of alcohol with a mortality of 41.7 per cent. Of those admitting excess there were eight, of whom two died. It may be stated that alcohol has been of no importance in this camp either in predisposing to pneumonia or in influencing the severity of the disease.

BACTERIOLOGY

Type determination was carried out in the laboratory by the Avery method with the artificial pneumococcus medium as described from this camp by Vaughan.[4] Certain minor modifications have been made during this period. The sputum from each patient was examined routinely on three successive mornings. It is improbable that a Type I, II or III organism would be concealed by a Type IV mouth organism on three successive cultivations. This is borne out by the fact that the organism found in pure culture in each pleural exudate has always been of the same type as that found in the sputum. Moreover, according to the figures of Krumwiede and Valentine[5] and of Beckler, Marden and Gillette,[6] who have controlled the Avery method by mouse determination, three cultures would make the results reliable.

The greater number of bronchopneumonia cases occurred during the early months of the camp and at a time when type determination was not being done. The laboratory reports during this period were not comprehensive and have not been included. Among the later cases, the pneumococcus has been found to be the infecting organism in seventy-seven cases. Sixty-four of these cases were typed, and of them fifty-five showed Type IV organism. Nine cases belonged to Type II. In twelve instances streptococci were found as the prevailing organism, and in six additional the pneumococcus and streptococcus were both present. Realizing that hemolytic streptococci had been reported as the cause of bronchopneumonia in several different camps, the laboratory personnel has made repeated attempts to find this organism. They have compared the organisms obtained here with cultures from another camp which has reported nearly universal *Streptococcus hemolyticus* cultures and find that it is not the same organism. The organism causing bronchopneumonia in the majority of cases in this camp is the pneumococcus, usually Type IV.

In lobar pneumonia the types of pneumococci found in 139 cases are distributed 82.1 per cent. to Type IV; none to Type III; 7.9 per cent. to Type II, and 10 per cent. to Type I. As we did not at first have Type III serum the first sixteen Type IV cases should more properly be classed as Type III or IV. Streptococcus was found in one case in association with a Type IV pneumococcus.

4. Vaughan, Warren T.: Type Determination of Pneumococcus Infection as Practiced in the Field with Avery's New Cultural Method, Jour. Am. Med. Assn., 1918, **70,** 431.

5. Krumwiede, Charles, Jr., and Valentine, Eugenia: Determination of the Type of Pneumococcus in the Sputum of Lobar Pneumonia, Jour. Am. Med. Assn., 1918, **70,** 513.

6. Beckler, Edith A.; Marden, Katherine, and Gillette, Helen H.: Pneumococcus Type Determination by Avery's Cultural Method, Jour. Am. Med. Assn., 1918, **70,** 836.

In several instances of pneumococcus culture both for lobar and bronchopneumonia the organisms have grown in short chains which to cursory examination might have been mistaken for streptococci. The diplococcus formation in the chain could, however, be well demonstrated.

Examination for tubercle bacilli has been routine and has been negative in every instance except one case of postmeasles bronchopneumonia. This patient died of a tuberculous bronchopneumonia.

Organisms in Pleural Exudate. — Pleural effusion occurred in twenty-four cases of lobar pneumonia that were typed. As a rule, clear fluids containing organisms will go sooner or later to pus formation. In but three cases showing organisms in the pleural exudate was operation not necessary.

CHARACTER OF THE PLEURAL EFFUSION IN TWENTY-FOUR CASES OF LOBAR PNEUMONIA

	Type of Pneumococcus			
Character of Chest Fluid	Type I No. Cases	Type II No. Cases	Type III No. Cases	Type IV No. Cases
Pus with organisms	2	1	0	10
Pus without organisms	0	0	0	2
Clear fluid with organisms	0	1	0	3
Clear fluid without organisms	1	1	0	3
Total	3	3	0	18

In regard to bronchopneumonia, the type of organism has been determined in the pleural exudate of eleven cases, in all of which it has been Type IV pneumococcus. *Streptococcus mucosus* has been found in one chest fluid and combined pneumococcus and streptococcus infection in one other. The empyema fluid from every bronchopneumonia typed since March 31 has shown pneumococci, except for two instances with *S. hemolyticus.*

Blood culture determinations have been made in thirty cases of pneumonia and have been sterile in all but three. There have been two positive cultures of Type IV pneumococcus and one of Type I.

LOBAR PNEUMONIA—SYMPTOMATOLOGY

As the first few cases were being treated and studied we were under the impression that the disease was not the classic pneumonia with sudden onset, chills, fever, pain, cough, rusty sputum and crisis. The following observations are convincing evidence that the pneumonia here treated is the same real pneumococcus lobar pneumonia with which all are familiar.

Character of Sputum.—In eighty-two the sputum was described, and of these, 81.8 per cent. had rusty sputum; 1.2 per cent., prune juice; 6.1 per cent., thick and tenacious, but not bloody, and 10.9 per cent., mucopurulent.

History of Chill.—In 50.8 per cent. of the 234 cases there was a history of sudden onset and chill. In 23.1 per cent. the history indicates that there was no chill. In the remaining 26.1 per cent. the information is indefinite. At least one-half and possibly as high as two-thirds of the patients, then, had a chill at onset.

Pain and Friction Rub.—Very nearly all complained of pain in the side. In five cases the pain was on the opposite side from that in which consolidation had occurred. Although the pain was pleural in character a friction rub was found in but 19.7 per cent. of the cases.

Character of Fever.—One hundred and ten patients ran a high fever with a mortality of 14.5 per cent. Of the sixty-five with a moderately high fever, 13.9 per cent. died. Thirteen had a moderate elevation of temperature, with no deaths. Of the eight who ran a low temperature, usually below 101 F., 37.5 per cent. died. The highest mortality is recorded in those running a low fever. The small number of patients in this class detracts from the value of the high figures, but these findings do correspond to the common statement that pneumonia patients with high temperatures and vigorous reaction to infection frequently do better than those running low temperatures. Of the three men who died after running a low fever, the first had had a moderate alcoholic history and developed a measles rash on the day of admission. No other complications occurred. The second had a consolidation of the entire right lung. The third was a casual admission from a passing troop train, had been sick six days before admission and was suffering from a consolidation of the entire left lung together with a left serofibrinous pleurisy.

Two-fifths of the patients had a typical crisis. Pseudocrisis was noted in eight instances. Two cases had a critical fall on the second day and one on the twelfth day. There were instances of crisis on every day intervening between these two extremes. The greatest number, however, was on the seventh day, being twenty-five, as contrasted with fifteen on the sixth and twelve on the eighth. As contrasted to eighty-eight instances of crises there were seventy-eight of lysis and in the remainder, the character of temperature fall could not be determined because of the incidence of complication or of death.

Lobes Involved.—As usual, the right lower lobe was consolidated most frequently. The other lobes in order of frequency were left lower, right upper, right middle and left upper. This is the usual order of frequency as may be seen by a comparison with the figures of Cross[7] covering 340 cases in the Minneapolis City Hospital. His order differs only in the fact that the left upper was involved more

7. Cross, J. G.: Analysis of Two Hundred Cases of Lobar Pneumonia, Jour. Am. Med. Assn., 1915, **65**, 1778.

frequently than the right middle. In our series there were one hundred instances of right-sided involvement, ninety-six of left involvement and nine of bilateral consolidation. In the five remaining, which were cases treated in the early days of the hospital, the lobe affected was not noted. The records show that the mortality increased regularly with increase in the number of lobes involved. In the two patients who had consolidation of four lobes 100 per cent. died.

Other Symptoms.—Abdominal tenderness of marked degree without abdominal complications occurred three times and the possibility of appendicitis was suspected in two additional patients. These were not operated on. *Nausea* was one of the early symptoms in eight instances and vomiting occurred in sixteen, of whom 19 per cent. died. *Abdominal distention* may be considered as of bad prognosis. Of nineteen cases with distention, approximately 50 per cent. died. *Icterus* occurred in nine instances. The mortality among those showing this symptom was 44 per cent. Severe *cyanosis* occurred in twenty-nine cases and delirium in twenty-one. Of the former, 45 per cent. died; of the latter, 33.3 per cent. Five cases were described as drowsy and all recovered. *Herpes* were noted on the lips seventeen times. Meningitis was suspected in four cases on which lumbar puncture was performed. There was no increase in the spinal fluid cell count and the patients subsequently ran typical courses of pneumonia. In all four cases the consolidation was right-sided and the right upper lobe was involved in three out of the four cases. The illness was severe in three of the patients, but only one died.

Duration.—The average duration of the stay in the hospital computed for 152 consecutive patients was thirty-three days.

BRONCHOPNEUMONIA

As has previously been stated, bronchopneumonia developed in the majority of instances after measles. There was usually no intervening period of good health, the ordinary postmeasles bronchitis became more severe, the temperature did not drop and the chest signs became more numerous. In thirty cases there was an interval of comparative good health and the patients had gone back to duty, but a careful questioning developed the fact that they were never well or entirely free from respiratory troubles during the interval. In two instances the pneumonia came on as long as thirty-three and thirty-five days after the patient had been discharged for measles.

Onset.—The onset of the pneumonic process was usually gradual. In only twenty-four cases was it sudden and in eighteen of these the differential diagnosis from lobar pneumonia was very difficult. Thirty patients, or 9 per cent., reported a chill at the beginning of their illness.

This chill was never severe and never seemed comparable in degree to that accompanying lobar pneumonia.

Character of Sputum.—The sputum was reported as being rusty in but three cases of this entire group. In these three cases the signs were those of bronchopneumonia and not of lobar pneumonia. Sputum was recorded as bloody in a few instances, and as greenish purulent in three. The vast majority of patients had mucopurulent sputum which was raised without great difficulty.

Cough and Hoarseness.—Cough was the most frequent single symptom. It was usually distressing, long continued and often provoked by motion, eating and drinking. In some cases it was markedly productive, while in others it was very scanty in its results. Hoarseness was recorded in one hundred and seventeen instances and 50 per cent. of patients in this group died. The symptom came early and lasted long after the patient was up and about the ward. In a few instances the hoarseness lasted for months. One such case is of interest, in that in view of the persistent hoarseness a Wassermann reaction was made and found to be strongly positive. The hoarseness had not been present before the onset of the bronchopneumonia. In these cases no lesion in the vocal cords, other than that of acute inflammation, was demonstrable.

Pain and Friction Rub.—Pain was not as frequent nor as persistent as was the case in lobar pneumonia. A friction rub was described in thirty-nine cases, and in these there was usually some associated pain.

Character of Fever.—In 265 patients the fever was either remittent or intermittent in type. Twenty-six cases had a continued type fever at some time during the course of the disease, but never throughout its entire extent. Many showed wide diurnal sweeps of temperature. This was especially true in the empyema cases. In 274 cases the temperature ranged during the height of the disease between 102 and 104 F. There was a single temperature record of 106 and a few over 105. The average duration of the fever for all the patients was fourteen days. Two uncomplicated cases had recurrent temperature for sixty days. At times the highest temperature record of the day was registered during the morning hours.

In but one case of pneumonia, diagnosed bronchopneumonia, was there a temperature fall by crisis. This patient had signs unmistakably against lobar pneumonia. In thirteen additional instances there was a critical fall of temperature, but it subsequently rose and continued irregular. In all of the remaining cases defervescence occurred by lysis over a more or less protracted period of time. Relapses were frequent.

Respiratory Rate.—In bronchopneumonia as well as in lobar pneumonia study of the pulse rate did not result in noteworthy findings. The important fact as regarding respirations was the low rate as compared with the lobar pneumonia. The majority of the patients had a respiratory rate around twenty-five per minute. Two hundred and forty-six men fell into this group. Respirations in bronchopneumonia, as well as in lobar pneumonia, have been recorded as high as sixty per minute before a fatal termination.

Physical Findings.—One of the characteristics of the physical findings in the bronchopneumonia patients at this camp has been their inconstancy and polymorphism. One-third of the series had bilateral râles which, at one time or another, were of nearly every description. Usually the coarse, moist râles of bronchial origin are transmitted to nearly all parts of the chest while the fine showers of pneumonic crepitation are limited to isolated patches. Signs of consolidation were fleeting and of uncertain size. In one-tenth of the cases bilateral râles of variable description furnished the only signs of pathology in the chest and in this series 33 per cent. died, a mortality practically identical with the general mortality. In two hundred and ten cases there were bilateral signs of consolidation. In some the signs were chiefly unilateral. One of the most frequent sites for consolidation lies to the vertebral side of either scapula. Consolidation is also frequently reported as being at the angle of the scapula.

Other Symptoms.—*Cyanosis* of marked degree was very frequently observed, especially in those desperately ill. Forty out of fifty-three severely cyanotic cases proved fatal. *Sweating* was frequently observed. The easily raised mucopurulent sputum, together with cyanosis and sweating, furnish a picture quite distinct from that seen on lobar pneumonia. *Herpes* was noted seven times, *jaundice* five times and *epistaxis* ten times. Nineteen patients were *delirious,* of whom eleven died. As a rule, one of the characteristics seen in our bronchopneumonia patients was a clear mental condition up until the time of death. *Distention* appeared in nine cases, of whom 44 per cent. died. The respiratory grunt characteristic of lobar pneumonia was never noted.

Course.—In regard to the course of the disease, there are three well-defined groups of cases. In the first group are those severely ill patients who at a very early period show signs of extensive and severe pulmonary damage and who die promptly, or more rarely, show early signs of improvement and finally recover. Fifty per cent. of our patients who were fatally ill died within ten days from the onset of their disease, while 75 per cent. died within less than fifteen days. The second type consisted of a protracted illness over a long period

of time and usually resulted in recovery. In this class complications were chiefly responsible for the long duration of stay in hospital. Comparatively few complications figured in the first group of cases. In the third class of cases were persons who had been moderately ill and who seemed to be convalescing favorably, but who experienced either one or many relapses. Some recovered and many did not. There were not necessarily complications in this class, although they frequently did occur. At times, there were few pulmonary signs to account for the relapse or for its severity. The presence of pus in the pleural cavity was frequently suspected and the record of unsuccessful needlings is evidence that this was not the cause.

Duration.—The average duration of stay in hospital for the 333 cases was between thirty-four and thirty-five days, a period surprisingly similar to that for lobar pneumonia.

DIFFERENTIAL DIAGNOSIS

It is natural that with so many cases of lobar and of bronchopneumonia, and with all grades of both conditions, it was at times extremely difficult to determine which disease was present. Physical signs may be atypical and unconvincing. The history may give no definite clue as to the condition. Certain rules, each having its exceptions, have aided in the diagnosing of these borderline cases. The *character of the sputum* was one of the most helpful aids. If it is thick, tenacious and especially blood-streaked or rusty, the involvement is presumably lobar. Of the cases of lobar pneumonia, 82 per cent. showed rusty sputum, whereas among bronchopneumonias, less than 1 per cent. of sputums were described as rusty. In this camp we found that with a history of *recent measles* infection and without an intervening period of fair health, the probability is that the condition is one of bronchopneumonia. *History of chill* with sudden onset is still characteristic of lobar pneumonia, being present in over 50 per cent. of cases, as contrasted with 9 per cent. in bronchopneumonia. The *fever* in lobar pneumonia is usually high and is more apt to be continued in character. In bronchopneumonia it tends to run lower and is frequently remittent in character, falling at times as low as 99 F., or even to normal. In the latter condition the diurnal variation is apt to be greater. Among the physical signs the presence of widely distributed, bilateral, medium and coarse, *moist râles,* and patchy distribution of constant sized crepitations of alveolar involvement are more definitely characteristic of bronchopneumonia than are the presence and distribution of definite signs of consolidation. We wish to emphasize the finding of Cole[8] who, in speaking of bronchopneumonia, states:

8. Cole, Rufus, and McCallum, W. G.: Jour. Am. Med. Assn., 1918, **70,** 1146.

In no uncomplicated cases have we seen wide areas of dulness with characteristic tubular breathing and other signs of consolidation. When these signs have been present there was always a complicating lobar pneumonia. In a few cases, however, later in the disease there has been impairment of the percussion note over a wide area, with quite distant tubular breathing over this area, but with voice sounds fairly well transmitted. The repeated insertion of a needle in these cases has failed to reveal fluid and the needle has felt as though it were in a more or less solid lung. We have interpreted these signs as due to a wide-spread involvement of the lung with a marked degree of proliferation and plugging of the bronchi.

We subscribe to the foregoing statement, but record one important exception. In our experience a patient with bronchopneumonia may have signs of consolidation over one entire base and not have lobar pneumonia. As was proved at necropsy in one such case, there was a massive empyema of that side with a completely collapsed lung, which was bound down to the posterior chest wall with pleuritic adhesions. In this particular instance sounds were also fairly well transmitted over the fluid. One further point noted by Cole is that there may be a combined infection and both types of pneumonia may be present in the same individual. Rarely the diagnosis may "hang fire" for many days, in which case the presence or absence of a temperature fall by crisis will aid in a decision.

COMPLICATIONS

Empyema.—This condition has been found as early as the second day of the disease. Here it is a question as to whether the empyema is not a primary condition, a question whether or not there is pulmonary consolidation behind the fluid accumulation. Two or three cases were admitted as pneumonia with a history of sudden onset with chills, fever and a pain in the side a short time previous to admission, and a history of measles a few weeks previously, who on physical examination showed, not the signs of pneumonia but those of fluid. Their general appearance and behavior also resembled pneumonia, but the presence of sweating suggested again purulent pleurisy. Thoracentesis on these cases bore out the diagnosis of empyema. There was no convincing evidence of accompanying pulmonary consolidation. Such cases seem to be the end-stages of a measles sequence. It is possible either that an unrecognized serofibrinous pleurisy was present from the time the patient was discharged after his measles, which had just become purulent, or that, as the result of the extensive damage done to the respiratory tract by the measles virus, there had occurred a primary empyema. The pneumococcus was found in the fluid.

Empyema may be present with a normal temperature. One patient who was entirely convalescent from his pneumonia and who had had a normal temperature for fourteen days was found, on the examina-

tion preliminary to discharge, to have one side of his chest entirely flat to percussion. Aspiration showed pus and at operation several pints of the material were drained.

Signs of fluid may be equivocal, but we have usually found them to be decidedly more definite in our cases of lobar pneumonia than in our bronchopneumonias. Flatness to percussion has been one of the two most reliable signs. With it there may be distant sounds or the bronchial voice sounds may be transmitted fairly distinctly. The breath sounds are less often transmitted through fluid than are the voice sounds. We have found cases of serofibrinous pleurisy with flatness, diminished tactile fremitus, absent breath sounds and distinctly transmitted bronchial whispered voice or egophony, in which the fluid was not purulent and there was no consolidation. The bronchial voice sounds presumably originated from a totally collapsed lobe. Flatness to percussion is not always present over fluid, especially so in the case of bronchopneumonia. Of equal importance to flatness on percussion is absence of or a very faint transmission of breath sounds even though there be but moderate dulness. This absence of complete flatness may be accounted for, perhaps, by presence of a fringe of lung tissue overlapping the fluid and tending to come between that and the chest wall. In favor of this supposition is the fact that very frequently it is necessary to insert the needle to a distance of 1½ inches or more before fluid can be reached. Opposed to this is the fact that no condition just like that described has been found at necropsy with the exception of some cases of interlobar empyema and of encapsulated pus in the pleural cavity adjacent to the mediastinum. Râles, usually coarse and sticky, may be present over an area containing fluid. It is never safe to say that because râles are present and seem close to the ear, fluid is absent. It is rare, however, to hear typical showers of fine, pneumonic crepitations over fluid.

The positions of the cardiac borders, apex impulse and point of maximum intensity of the heart sounds are of great importance. Diminished respiratory excursion on one side is most suggestive of fluid accumulation in considerable amount on that side. The patient's general condition is of aid in arousing the suspicion of fluid, but does not enable one to make the diagnosis. The typical septic appearance, the flushed cheeks, the moist skin, a slightly icteric tinge to the skin and the presence of sweating, especially at night, are the points of importance. In lobar pneumonia the presence of sweating had been of material benefit. In bronchopneumonia this feature is frequently present without empyema and due presumably to the purulent bronchitis.

Determination of the presence or absence of Grocco's paravertebral triangle has not given great assistance. The roentgen ray has been

helpful in some cases, but it has not increased materially the number of instances in which fluid has been found. In but one class of cases has the roentgen ray been indispensable, namely, interlobar empyema and allied conditions.

In this camp, as at other camps, collections of pus have been found at necropsy substernal, in the mediastinum, and in the pleural cavity between the lungs and the pericardium or mediastinum. The roentgen ray has enabled us to find these encapsulated fluids in time to treat them. For example, one patient was tapped early in his illness and 15 c.c. of a serofibrino-purulent fluid containing pneumococci was withdrawn. The fluid was not found until the needle was inserted to its full length. Several subsequent thoracenteses were nonproductive. Later, after the acute condition had subsided and the temperature was running from normal in the morning to 99 or 101 F. in the afternoon, the roentgen ray showed a shadow between the mesial surface of the right lower lobe and the pericardium. A needle was then inserted deep into the eighth right interspace, 8 cm. from the spinous processes, and thick, creamy pus was withdrawn. Thoracotomy was done and the patient is now about ready for discharge. We have another patient in the ward at present, convalescent from bronchopneumonia, who has the classic signs and symptoms of an abscess in the mediastinum with substernal pain, increase in retrosternal dulness, a mediastinal shadow shown by the roentgen ray, unequal pupils and pulses, and the constitutional signs of pus.

Too great emphasis cannot be placed on the statement that if one is convinced from the signs and general condition that fluid is present, needling should be persisted in even though no fluid be at first obtained. One example will suffice.

A patient who had lobar pneumonia was suspected of having fluid extending from the region of the cardiac apex around to the region of the left scapular angle. A needle was inserted in this latter area and no fluid was obtained. It was then inserted in the fourth intercostal space anteriorly, about 5 cm. outside of the nipple. No fluid was obtained. It was immediately reinserted one interspace lower, not 1 inch from the previous point, and a purulent fluid was withdrawn. Two hours later, at operation, over a pint of pus was drained from this region.

Another maneuver in the successful demonstration of fluid is in directing the needle in more than one direction after it has once been inserted. One more point to be borne in mind is that, before tapping the patient should be so placed that the suspected area is as nearly as possible the dependent area.

Encapsulated fluid has seemed to be the rule rather than the exception. The cases described in the foregoing serve as examples. In truth, there is scarcely an area in the chest surface, with the exception

of the precordium and the apices, from which we have not been able in one case or another to obtain fluid. In one case of lobar pneumonia in which we were convinced that pus was present we obtained it only through the region of the right nipple. At operation the surgeons preferred to perform a posterior rib resection. No pus was obtained and it did not appear until a secondary operation was performed when the adhesions were well broken up. Occasionally, encapsulated fluid will occur in two separated areas in the same chest.

Patients who had bilateral empyema, of which we have had seven, have not recovered.

We have generally been able to find fluid before it has become purulent and have been able by repetition of needling to determine the most desirable time for operation. This optimal time is a question on which there is still considerable difference of opinion. Some cases of serofibrinous pleurisy have been sent to the surgeons as soon as the fluid has been proved to contain organisms. The reason for this early transfer was the argument that the condition, provided organisms were present in the fluid, was somewhat analogous to that of an acute appendicitis in which one would invariably operate by preference long before the development of frank pus. In other cases we have waited until the fluid has become purulent. Out of twenty-one patients in whom the fluid at operation was of the former type, eleven died. Out of nineteen in whom it was described as definitely purulent, but two have died. We feel that the best procedure is to tide the patient through the acute pneumonia by complete aspiration as long as the fluid is relatively clear, and after that to continue aspirations if the patient is improving, otherwise to operate. In some instances the critical condition requires an early operation. This is especially true in bronchopneumonia, in which condition the fluid may never become pus, the patient dying before that time. Operation has, therefore, been done earlier on such critical cases and sometimes has without doubt been a life-saving procedure. Rib resection has been the operation of choice, although in some of the severely ill a thoracotomy has been done. The results with our patients who were operated on for empyema have been fairly satisfactory, the mortality being about 28 per cent.

There are two periods during the course of acute lobar pneumonia at which the signs may very strongly suggest a pleural effusion which is, in reality, not present. The first is early in the disease when the signs of consolidation have not developed fully and when there may be dulness but usually not real flatness, with suppression of the breath and voice sounds. If the beginning consolidation is in the lower lobe, fluid may be strongly suspected. In fifteen of our cases these signs were present. The second and more important period is

at or about the time of crisis and resolution. Following the presence of dulness, bronchial breathing and bronchophony, there may develop distant bronchophony and dulness to flatness over the same area. Thoracentesis will be nonproductive and on the same day or soon thereafter, the temperature will suddenly drop to normal where it will remain. We know of no accepted anatomic explanation for this phenomenon, but suggest that with beginning resolution more air enters the central portion of the lobe, in the region of the larger bronchi, and consequently the bronchial breathing and bronchophony become less distinct. The still considerable amount of consolidation accounts for the persisting dulness. As the resolution progresses this dulness also clears up. We have had twelve such cases in which fluid was suspected and some of which were tapped with negative results.

One notable difference between the bronchopneumonias of this camp and of certain other camps is in the comparatively lower incidence of empyema. There have been until March 31, but twenty-nine cases of post-bronchopneumonia empyema. Of twenty-six necropsies on bronchopneumonia patients, but ten had empyema. Nearly all of these were postoperative cases. In the ninety-four earliest cases of bronchopneumonia in which the patient died no necropsy was made. These may have had a high proportion of empyema. But among the two hundred and thirty-nine who either recovered or were examined at necropsy, the incidence of empyema was 8.2 per cent. The true percentage was not lower than this figure and presumably was several points higher on account of possible empyema in the ninety-four cases in which no necropsy was made. We cannot give definite figures as to the percentage of empyemas following bronchopneumonia, but draw attention to the fact that the apparent relative infrequency of empyema corresponds well to the fact that the pneumococcus, rather than the hemolytic streptococcus, was the infecting organism. The empyema percentage in lobar pneumonia was 13.5.

Pericarditis. — This complication occurred in nine cases in the series. There have been three additional instances in more recent cases. It is of bad prognosis. Of these twelve patients, nine died, one is still seriously ill and the other two, after a stormy illness, recovered. In the majority of instances pericarditis is a terminal complication.

Urticaria.—This condition has occurred as a part of serum sickness in cases treated with Type I antipneumococcus serum. It has also occurred in two instances of the lobar pneumonia series and in three additional cases since March 31, when no serum has been given and no cause could be found. In these latter cases the rash usually came out around the time of crisis, and we suggest that it may be an evidence of sensitization reaction, either to the proteins of the pneumo-

coccus or to some protein derived from the exudate itself. Allied to this is another case diagnosed as idiopathic purpura in which there developed cutaneous manifestations, similar in character to erythema multiforme. There was an accompanying spontaneous bleeding from the bowels. No cause was discovered. Rectal examination was negative, except for some tenderness high up. The patient had two attacks at short intervals and was discharged in good health

Peritonitis.—As a complication of lobar pneumonia we have had, in the series quoted, one case of peritonitis as shown at necropsy, and, since March 31, we have had three additional cases. The first, at necropsy, had not only a purulent peritoneal exudate, but also pus in both pleural cavities and in the pericardium, a condition which we choose to designate for lack of a better term, as suppurative polyserositis. One or two other patients have been in the wards in whom peritonitis had been very strongly suspected. The patients died, but necropsy could not be performed.

Two of the peritonitis cases are of interest as being postoperative. The first of these was operated on for appendicitis and developed a postoperative pneumonia which was, in turn, followed by general peritonitis and death. At necropsy the consolidation was found to be in the stage of resolution. The interesting feature was that a culture of the peritoneal exudate showed the infection to be pneumococcic. In the second case, several days after an appendix operation, lobar pneumonia developed, which was followed by a pneumococcus empyema, a general peritonitis and death. The appendix scar had nearly healed over. Here again pneumococci were found to be the invading organism of the peritoneum.

The symptoms of peritonitis, complicating pneumonia, are usually quite indefinite. There is more or less abdominal distention and some tenderness on pressure. Muscle spasm may be slight or absent. The pathologic picture is one of a thin layer of yellow greenish pus covering various portions of the intestines and found particularly between coils and down in the folds. There is very little accumulation of peritoneal fluid.

Arthritis.—Following lobar pneumonia the acute suppurative form of synovitis, as well as cases with the classic symptoms and signs of acute rheumatic fever, have been noted. Pneumococci were isolated from the joint of two of these cases with suppurative synovitis. Salicylate did not appear to have great effect on the "rheumatic fever" type of case.

Other Complications.—There have been several cases which have developed *multiple complications,* so that the patients have had to remain in the hospital for months. One patient, after a pneumonia of the right lower lobe, developed a right empyema, a fibrino-purulent

pericarditis, an empyema of the left pleural cavity and finally died. At necropsy there was found, in addition to all of this, a purulent mediastinitis. Another patient who had been convalescent for seventeen days from lobar pneumonia, involving the left lower lobe, developed a bronchopneumonia with a right-sided empyema and died. Pneumococci, Type IV, were found in the pleural exudate. Another sequence reported is of measles, bronchopneumonia, purulent otitis media, empyema, terminal lobar pneumonia of the opposite side and death. Yet another individual, admitted with a postmeasles otitis media, later developed a mastoiditis which was operated on. Then followed a post anesthetic lobar pneumonia, a right serofibrinous pleurisy without organisms, an acute purulent synovitis of the right shoulder joint and finally mumps. This patient was also a hookworm host and this may have accounted in part for the numerous complications. He was later discharged well.

Among others of the more important complications of both forms of pneumonia, may be mentioned serofibrinous pleurisy, otitis media, mastoiditis, laryngitis, an anaphylactic reaction to intravenous serum in four cases, and metastatic interstitial abscesses. Otitis media and mastoiditis deserve further mention. They were of rather high incidence during December and early January, but in the latter half of our series these complications have been decidedly less frequent. Among the lobar pneumonia patients right otitis media occurred ten times, left involvement six times and bilateral involvement in five instances. Five cases progressed to mastoid involvement. Among the bronchopneumonia patients there were fifty-eight cases of otitis media, with twenty-four in the right, twenty on the left and fourteen bilateral. Seventeen cases of mastoiditis resulted therefrom.

PNEUMOCOCCOSIS AT CAMP SEVIER

Not only has the laboratory force been unable to demonstrate the presence of the hemolytic streptococcus in the cases of bronchopneumonia, but also they have found that the pneumococcus at this camp might aptly be termed omnipresent. We have had five cases of pneumococcus meningitis, not secondary to other disease. One of these was due to Type I pneumococcus. We have had cases of primary otitis media and mastoiditis in which the pneumococcus was found in pure culture. There is one patient in the hospital suffering from a spondylitis and a psoas abscess. Type I pneumococcus was found in pure culture in the pus. There are two patients with a Type I pneumococcus infection in the form of a chronic bronchitis. The organism in both of these cases has been obtained directly by lung puncture. During a meningitis survey of several companies of the division, the pathologists have frequently found nearly pure cultures of pneumococcus in the nasopharynx. Many other instances might be included.

SPECIFIC TREATMENT

In view of the good results reported from treatment of Type I pneumonia with Type I immune serum we have grouped all cases of pneumonia admitted since the middle of December, 1917. Type determination with the use of the mouse is, admittedly, the more accurate method and should be employed wherever practicable. In the absence of mice we have used Avery's cultural method with satisfactory results. Emphasis should be placed on the desirability of making repeated sputum cultures on the same patient. Every report of Type IV pneumococcus is a negative report. It means that, other than the presence of the diplococcus, nothing definite was found. We have insisted on at least three type determinations on every patient. Perhaps the greatest disadvantage in the method is in the fact that occasionally a Type IV report is followed the next day by one of Type I on the same patient and a day is thus lost for serum treatment. We have taken the three specimens on three successive days. We recommend that it would be much better to take them all on the first or first and second days. Careful collection of real sputum and careful washing thereof will eliminate nearly all of this trouble.

In the treatment of Type I cases with homologous serum, desensitiation and intravenous administration were carried out according to the technic outlined by Avery, Chickering, Cole and Dochez.[9] We found certain precautions to be essential: (1) The first 15 c.c. should be given very slowly, taking in all about fifteen minutes. If this procedure is followed there is very little danger, even with sensitive patients; (2) watch the respirations, and if they become accelerated, discontinue administration until it can be determined whether this is a beginning anaphylactic reaction, and (3) watch for evidences of peripheral irritation and for urticaria.

In from five to ten or more minutes after serum has been given intravenously to a sensitized individual, he will evidence slight uneasiness. He may rub his heels on the sheet or his legs against each other. He may scratch various portions of his body while complaining of the tingling. Or his first symptoms may be respiratory. His breathing will gradually increase in rapidity. If the nurse has her elbow over the patient's chest or abdomen he may push it aside, complaining of the weight or that it interferes with breathing. The respirations increase until the breathing is rapid, deep and labored as when one has just finished a hard run. It is not the shallow panting of an hysterical individual, nor has it exactly the typical wheezing expira-

9. Avery, Chickering, Cole and Dochez: Acute Lobar Pneumonia, Monographs of the Rockefeller Institute for Medical Research, No. 7.

tions of the asthmatic. The impression is given of a great increase in pulmonary ventilation. Respirations may become so labored that the patient cannot reply to questions. He is alert and apprehensive. As the dyspnea becomes very marked moderate cyanosis develops. By this time urticaria is usually quite widespread. If in the region of the eyes they may swell nearly shut. This anaphylactic reaction is combated by immediate discontinuance of serum administration and the intramuscular injection of atropin and epinephrin. The patient rapidly improves and in fifteen minutes from the height of the reaction appears none the worse for the experience. It is advisable not to give additional serum within less than one hour's time.

Type I pneumonia, as has been previously noted, has been rather infrequent in this camp. Ten per cent. of the lobar pneumonias were infected with this organism, while none of the bronchopneumonias were so infected. Ten cases have been serum treated. Four cases treated early in the disease had a temperature fall to around normal within twenty-four to thirty-six hours and with immediate amelioration of symptoms. They did not suffer any relapse. One patient with consolidation of the right upper lobe had a crisis with a normal temperature on the third day. That evening a temperature of 104 F. developed, and the inflammation spread to the right lower lobe. Two serum administrations brought the temperature to below 100.5 F., from which it did not again rise.

In the case of one patient 90 c.c. of serum were given on the sixth day. At the end of twelve hours the patient had passed through the crisis. Convalescence was uninterrupted. One further case, first treated on the fifth day, was given two 100 c.c. doses and the temperature reached normal within twelve hours from the last administration. A subsequent serous effusion, without organisms, appeared and disappeared without requiring special treatment. One case who had previously developed fluid with organisms in his chest improved markedly under serum treatment, but did not recover completely and rib resection was subsequently done for the empyema. He recovered. He had been extremely ill and serum undoubtedly was the means of saving his life.

Two of our serum treated patients died. The first case did not receive serum until at a time when he was moribund and after he had developed a massive empyema. The other patient had received a sufficient amount of serum, 500 c.c. in all, but did not respond to treatment and died without any recognizable complications having occurred. Treatment in this case was also instituted rather late. A necropsy unfortunately could not be obtained.

Type I immune serum is a most valuable addition in the treatment of pneumonia. It should be used in all cases of Type I infection; the

earlier in the course of the disease the more satisfactory will be the results.

Polyvalent serum was used in a few cases of severely ill bronchopneumonias and without beneficial results.

MORTALITY

In lobar pneumonia the mortality for the entire period from the opening of the hospital until March 31, 1918, was 14.9 per cent. Our highest number of deaths occurred during the early days of the hospital. In a period from December 1, 1917, until March 31, 1918, during which more accurate records were kept, type determination was made, better methods of isolation were employed and the treatment was supervised in all wards by one individual, the mortality was decidedly lower, being 10 per cent. In this second period nearly all of the cases fall, 201 out of 234. Ten per cent. should, then, be more properly the average death rate from the disease in this camp. Among those earlier cases in which the patient died, the records at times leave some doubt as to the possibility of the death being due to an intercurrent, or a primary empyema, rather than to lobar pneumonia.

The death rate with Type I pneumonia is recorded as 14 per cent., and from Type IV as 7 per cent. There were no deaths among the eleven cases of Type II pneumonia. The Type I mortality includes both serum treated cases and those not so treated.

In bronchopneumonia the death rate has been 36 per cent.

CONCLUSIONS

It is a generally recognized fact that statistical reviews are subject to erroneous interpretation and may lead to false conclusions. Yet without such compilations in the past, the progress of medical knowledge would have been considerably retarded. We have felt that a study made by the persons who have had in charge the care and treatment of the cases and who have been led into definite points of view from personal contact with the patients, will be of greater value than a compilation of statistics from various observers in numerous camps. The authors have therefore undertaken to present their experiences and conclusions regarding pneumonia and empyema at Camp Sevier and to verify these findings with the use of figures. From our observations we are led to conclude that the pneumonias as seen in this camp do not comprise an hitherto unknown form of disease, but are in essentials, the same clinical types of the diseases as have been previously described.

THE TREATMENT OF BRONCHIAL ASTHMA WITH PROTEINS *

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In a recent paper[1] many important clinical facts were brought to light from the study of a series of 400 patients with bronchial asthma. These facts all have a direct bearing on the determination of the cause of the condition and therefore indirectly they indicate the proper treatment. Among other facts, it was shown that 48 per cent. of the 400 patients were sensitive to some type of protein and that the younger the patient was when he began to have bronchial asthma the more apt was he to be sensitive to some protein. A table was presented showing the number of patients who were sensitive to the four chief sources of protein, namely, animal hair, food, bacteria and pollens, at the various ages of onset of bronchial asthma. The skin or cutaneous test was employed to determine whether or not the patients were sensitive.

The object of the present paper is to give the results of the treatment of sensitive patients with the proteins to which they were sensitive. Incidently the relative importance of positive skin tests with various proteins in the same patient will be shown. Only those patients who were sensitive to the proteins in animal hair and in food will be included in this paper. The method of performing the skin test has been frequently described so that it will be omitted here; however, it should be said that in this paper a reaction to be called positive must present an urticarial wheal measuring at least 0.5 cm. in diameter. Therefore, as regards the proteins of animal hair and foods, these must give a definite reaction in order to be called positive; smaller reactions should be noted and repeated and frequently they give valuable information; but in this paper, to be conservative, small reactions are ignored. The method of treatment of the sensitive patients will not be given in detail since this has been described in previous papers.[2]

In the series of 400 patients, 67 were sensitive to the proteins of

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* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Walker, I. C.: A Clinical Study of 400 Patients with Bronchial Asthma, Boston Med. and Surg. Jour., 1918, **179,** 288.

2. Walker, I. C.: The Treatment of Patients with Bronchial Asthma with the Proteins to which They Are Sensitive, Jour. Med. Research, 1917, **36,** 423.

Other papers on the study of bronchial asthma made possible through a gift by Mr. Charles F. Choate, Jr., of Boston, to the Peter Bent Brigham Hospital are as follows: Studies I-V, Jour. Med. Research, 1917, **35,** 373, 391, 487, 497, 509; Studies VI-VIII, Jour. Immunol., 1917, **2,** 227, 237, 243; Study IX, Am. Jour. Bot., July, 1917; Studies X-XIII, Jour. Med. Research, 1917, **36,** 231, 237, 243, 295; Study XIV, ibid., **36,** 423; Study XV, ibid., 1917, **37,** 51; Studies XVI and XVII, ibid., 1917, **37,** 277, 287; Study XVIII, Jour. Am. Med.

horse dandruff; that is, 17 per cent. of the whole series and 35 per cent. of the total sensitive cases were sensitive to horse dandruff. Of the 67 patients, 48 were treated with desensitizing doses of horse dandruff proteins with the following results: 30 patients were relieved of asthma, 8 were not improved at all, 5 have been treated too short a time to warrant a definite prognosis, and in the remaining 5 cases it is difficult to state how much the improvement was really due to horse dandruff treatment, because other treatment was given at the same time. Therefore, of the total patients who were both sensitive to and treated with horse dandruff proteins, in 63 per cent. there was relief from asthma; in 20 per cent., because of other or of insufficient treatment, it is impossible to state the results of horse dandruff treatment, although in these cases such treatment cannot be considered a failure, but in the remaining 17 per cent. horse dandruff treatment was a failure as regards the relief of asthmatic attacks, and therefore only in this 17 per cent., or 8 cases, one might conclude that the skin test was misleading. Five of these patients, however, were sensitive to, and were relieved by, the omission of wheat, and in these 5 patients there was no indication for treatment with horse dandruff, since the positive skin tests with wheat explained the cause of asthma; horse dandruff treatment was given only to see whether or not it would desensitize against wheat, and it did not, thus showing a specificity in the protein treatment. Therefore, in only 3 cases did positive skin tests fail to explain the cause of asthma.

In a previous paper[1] the importance of the age of onset and the duration of asthma was emphasized; therefore, it might be well briefly to summarize these facts as concerns those patients who were relieved by treatment with horse dandruff proteins.

In 8 patients attacks of asthma began at approximately 1 year of age and the duration, at the time treatment was begun, varied between six and thirteen years; 2 patients had had asthma for 13 years, 3 for 11 years, the other 3 for 6, 7, and 9 years, respectively. In 5 cases, asthma began at approximately 2 years of age and the duration at the time of beginning treatment was from 8 to 28 years; the actual duration in each case was, respectively, 28, 25, 12, 10, and 8 years. In 7 patients the onset of asthma was between the ages of 3 and 5 and the duration up to beginning of treatment was from 6 to 31 years, or, respectively, 31, 16, 15, 10, 7, 6, and 6 years. In the remaining patients the age of onset was at 9, 10, 12, 22, 23, 26, 40, and 43 years of age and the duration was, respectively, 20, 23, 32, 1, 25, 5, and 2 years. Therefore, of the 30 patients who were sensitive to and relieved by horse dandruff proteins, 8 began to have asthma at the age of 1 year,

Assn., 1918, **70,** 897. The Cause and Treatment of Bronchial Asthma, Med. Clinics of North America, Boston, 1918, **1,** No. 4.

5 at the age of 2 and 7 at the age 3 to 5 years; in other words, two-thirds began to have asthma previous to the age of 5 and only 2 patients began symptoms after the age of 26. Since in 9 cases the duration was from 20 to 32 years, and in 15 cases the duration was from 6 to 13 years, there is no chance for doubting the good effects resulting from horse dandruff treatment; one can hardly say that the patient outgrew, or incidently ceased having, asthma.

Another indication of the benefit derived from desensitization with horse dandruff protein is the reduction in the positiveness of the skin test with that protein. Usually the positiveness of the skin test diminishes as the amount of protein in the treatment increases, provided the increase in the treatment is slow and gradual; if, however, treatment is rapidly increased, the skin test and the patient's desensitization cannot keep pace with the treatment and sooner or later a larger amount of protein will be given than the patient is able to stand, and consequently he may have symptoms of anaphylactic shock. If treatment is carried on for a long time and in the proper manner the positiveness of the skin test will greatly decrease and will eventually become negative. The following cases illustrate this point: Case 1 before treatment, 1:100,000 positive, after 22 treatments only 1:100 was positive; Case 2, before treatment 1:100,000 positive, after 23 treatments 1:100 positive; Case 3, 1:100,000 positive, after 41 treatments 1:100 positive; Case 4, 1:10,000 positive, after 51 treatments 1:100 negative; Case 5, 1:10,000 positive, after 20 treatments 1:100 positive; Case 6, 1:10,000 positive, after 14 treatments 1:100 positive. A total of 900 treatments has been given with the proteins of horse dandruff and to the 30 patients who were relieved of asthma a total of 675 treatments was given. It is too early to predict the duration of desensitization or the permanancy of relief by such treatment; however, we do know that following a few treatments the patient is apt to relapse a few months later, but after many treatments so far no patient has relapsed. In one patient two years have elapsed, and in four others from eighteen to twenty months have elapsed without a relapse. In this research work the individual proteins in horse dandruff have been used, and it has been learned that patients vary in their degree of sensitiveness to these different proteins, and, furthermore, treatment with one of them does not desensitize against the others. The peptone and the protein are the two constituent proteins of horse dandruff that are absolutely necessary for such work, and it would seem that the other constituents are not necessary, so that for tests and treatment these two proteins should be used either separately or in equal parts together; the latter is of course the handiest to use. Patients naturally will not be so sensitive to a combination of the two proteins as to either one separately; therefore, instead of a positive skin test with a dilution

of 1:10,000 or higher, as is usually the case with either one of the proteins alone, these higher dilutions will be negative with a combination of them unless the patient is very sensitive to both.

Since one might ask why nineteen patients who were sensitive to horse dandruff protein were not treated with them, a brief discussion of these cases is indicated. Five of the patients lived too far away to be available for weekly treatment. All were children or young adults, and three of them knew that exposure to horses caused asthma. Four others had attacks of asthma only when they were near horses and as these patients (all adults) were able to avoid close proximity to horses, treatment seemed to be unnecessary. Furthermore, they were not sufficiently sensitive to warrant treatment. They gave positive skin tests with the dandruff proteins in dilutions no higher than 1:100; therefore, such patients would not be exposed to enough dandruff protein in ordinary walks of life to cause trouble; the patients would have to be closely associated with horses to have trouble. Patients who are so sensitive to dandruff proteins that dilutions of 1:10,000 or 1:100,000 give a positive skin test (and this is frequently the case) we feel should be desensitized, because the dust from city streets probably contains enough dandruff protein to cause attacks in such highly sensitized individuals. Two patients, aged 23 and 28, who had had asthma for nineteen and ten years, respectively, were much more sensitive to cat hair proteins than to horse dandruff proteins, and as they did not wish to part with their pet cats, they were treated with and were relieved by cat hair proteins. One patient who had had continuous asthma for sixteen years, beginning at the of 18 months, was very sensitive to wheat proteins, and omission of wheat from the diet relieved her asthmatic condition. She knew that horses did cause her to have asthma, but she could avoid them. One patient who was not very sensitive to horse dandruff was extremely sensitive to feather protein, and he had asthma only when he slept on a feather bed. Two patients, aged 31 and 27, had had asthma for thirty and ten years, respectively, but they were not sensitive enough to be treated with horse dandruff; they were relieved by vaccines. The remaining four patients all had attacks of asthma when intimately in contact with horses, but they were not considered sensitive enough to treat, and, furthermore, on account of their bronchitis, vaccines seemed to be indicated. Their ages were 64, 63, 58 and 51, and they had had asthma for 60, 63, 7 and 20 years. In the first two cases asthma began at the ages of 1 and 4, and the first attacks in each case resulted from exposure to horses. Therefore, in all of these nineteen cases there was a definite reason for not attempting desensitization with horse dandruff protein, and yet there was enough evidence to confirm the positive skin tests with this protein.

In the whole series there were twenty patients who were sensitive to the protein in cat hair, but of this number only four were treated with cat hair protein, and of these a total of 113 treatments were given. Two of these patients were relieved by such treatment; one patient was 38 years of age and had had asthma for ten years, and the other, who was 28 years old, had had asthma for six years. The latter patient gave a positive skin test with cat hair protein in a dilution of 1:1,000,000 before treatment, and after twenty-four treatments the skin test was positive with only a 1:10,000 dilution of cat hair protein. This patient then went a year without treatment, and it is interesting that after a year without treatment the skin test was still positive with a dilution of 1:10,000; the patient has now gone a year and a half without treatment and she has been free from asthma all of this time. The first patient gave a positive skin test with cat hair proteins in a dilution of 1:100,000 before treatment; after thirty-eight treatments with cat hair protein the skin test was only slightly positive with a dilution of 1:1,000 of this protein, but the skin test remained the same for cat hair peptone, which was still positive in a dilution of 1:100,000. Twenty-three treatments were then given with cat hair peptone, and the skin test was reduced to positive with a 1:1,000 dilution. This patient shows well the specificity in the protein treatment of asthma, in that treatment with the protein alone did not change the positiveness of the skin test for peptone, and the case also shows the necessity of using both the protein and the peptone either separately or in equal parts together for tests and for treatment. Although this patient also has been free from asthma for eighteen months, treatment with the cat hair proteins is still being continued. The third treated case was that of a young girl who lived on a farm among cats and horses. Twenty treatments were given with the protein of cat hair without relief from asthma. Treatment was then begun with the protein of horse dandruff and the patient rapidly became free from asthma. Thus, this patient also well illustrates the specificity of protein treatment for asthma, since treatment with cat hair protein produced no benefit, whereas treatment with horse dandruff protein relieved the condition. The fourth treated patient was a woman, aged 42, who has had asthma for nineteen years. Since she has had only ten treatments, it is too early to prognosticate; still she has gradually improved until she is free from asthma. Therefore, of these four patients who were sensitive to and treated with cat hair protein, two were relieved, one is practically relieved during a small number of treatments, and the other, who did not improve under treatment with cat hair protein, was relieved by horse dandruff protein, so that there really were no failures either in treatment or in the skin tests.

The remaining sixteen patients, who were sensitive to cat hair proteins, were not treated with these for the following reasons. Three

patients disposed of their cats and therefore desensitization with cat protein seemed unnecessary. Three patients were sensitive to wheat and were relieved by omitting wheat from the diet. Eight patients were so much more sensitive to horse dandruff than to cat hair that they were treated with horse dandruff protein and were relieved. The remaining two patients were more sensitive to other types of proteins, although they knew that attacks of asthma had directly followed petting cats. There seems to be no evidence for doubting skin tests in these cases.

Nineteen patients were sensitive to the proteins in dog hair, but none was sensitive enough to require treatment; one patient gave a positive skin test with a dilution of 1 : 1,000 and all others only with a dilution of 1 : 100. None was sensitive to dog hair alone and all were very sensitive to horse dandruff, so that treatment was given with the latter; several were also somewhat sensitive to cat hair protein. In only two patients was there evidence that asthmatic attacks directly followed intimate contact with dogs. The infrequency of asthma from dogs and the slight degree of sensitiveness to their hair is probably explained by the fact that pet dogs are frequently bathed and are kept clean, and that the unkept street dog is not a pet, but more or less wild.

Only a rare case was sensitive to the hair of cattle, and in one instance attacks of asthma definitely followed intimate contact with cows; all of these patients were very sensitive to horse dandruff protein. The same holds true for wool. Sensitization to feather protein is fairly frequent but certainly not nearly as frequent now as in former times when feather mattresses were in vogue. In this series of cases three patients definitely had asthma from feathers, and when the feather pillows (in two cases) and feather mattress (in one case) were discarded asthma ceased. Therefore, although cattle hair, wool and feathers are not frequently the cause of asthma, yet they may be a cause, and they surely should always be considered in obscure cases.

It is thus seen that patients who are sensitive to the proteins in one type of animal hair are also frequently sensitive to the proteins in other types of animal hair. Such patients, however, are far more sensitive to some one type of animal hair than to the others, and it is with that protein to which the patient is most sensitive that treatment should be given provided the patient is not more intimately in contact with some animal hair which gave a lesser degree of sensitization. Circumstances alter cases, and treatment may be a matter of judgment. In the case of feathers and wool, avoidance of the causative agent is simpler than treatment with it, and to a certain extent this holds true for cats and dogs. It is practically impossible for one who is very sensitive to horse dandruff to avoid horses and horse dust in the street sufficiently well to prevent trouble.

Thirty patients (7.5 per cent. of the total number of cases, and 15.7 per cent. of the total sensitive patients) were sensitive to the protein of the cereal grains. Twenty of these were sensitive to wheat alone, 5 to wheat and other cereals together, and 5 to the cereals other than wheat. The order of frequency of sensitization to the cereals, exclusive of the 5 patients who were sensitive to all cereals, was as follows: Wheat, 20 cases, or 64 per cent.; corn, 6 cases, or 20 per cent.; rice, 3 cases, or 10 per cent.; rye, 2 cases, or 6 per cent. Sixteen of these patients were also sensitive to other types of proteins such as animal hair, pollens or other foods; however, as the cereals contain the most common protein that enters the body, these should first be eliminated.

Of the 20 patients who were sensitive to wheat alone, 15 were relieved of asthma when wheat was omitted from the diet; all 5 of those who were sensitive to all the cereals, including wheat, were relieved of asthma when all cereals were omitted from the diet; and of the 5 patients who were sensitive to cereals other than wheat, 2 were relieved by the omission of these cereals. Therefore, in 75 per cent. of the patients who were sensitive to cereals, the positive skin test was confirmed by the therapeutic test, namely, relief from symptoms when cereals were omitted from the diet. Of the patients who were relieved, 9 began to have asthma at the age of 2 years or under, and they had had asthma from 8 to 28 years; 4 began asthma between the ages of 3 and 5, and the duration of asthma was from 14 to 20 years; 6 began to have asthma in young adult life, and the duration was from 8 to 19 years; the remaining 3 patients were bakers who began to have asthma at 35, 37 and 40 years of age, and the duration was 7, 15 and 1 years, respectively. Therefore the younger the patient is when asthma begins, the more essential it is to test with the cereals, and since the duration of asthma in those relieved varied from 8 to 28 years, the relief following the omission of cereals from the diet would not seem to be accidental, or due to some other influence. Also the importance of testing bakers with the cereals is brought out.

Eight patients who gave positive skin tests with the cereals were not relieved by the omission of these from the diet. One patient, a foreigner who understood very little English, gave a positive skin test with the cereals, rye, rice and corn, but while these were omitted from the diet no improvement was noted; she was 31 years old and had had asthma for 15 years. Another patient, aged 33, who had had asthma since infancy, gave positive skin tests with wheat and corn, but she showed no benefit while these were omitted from her diet. A third patient was a baker, aged 50, who had had asthma for 9 years; he was sensitive to all of the cereals, yet the omission of these from the diet resulted in no benefit. This patient was greatly improved by

vaccine treatment. Two other patients, young adults, gave positive skin tests with corn protein alone, but there was no evidence that the ingestion of corn caused trouble, and they both were relieved of symptoms by other treatment. Two patients, aged 42, gave positive skin tests with only one of the wheat proteins, namely the albumin, leucosin, but with none of the other proteins of wheat. One of these patients was relieved of asthma by vaccines and the other was not benefited at all; both had had asthma for twenty years. The remaining patient was a young girl who had had asthma since infancy; she was sensitive to horse dandruff, wheat and egg. This patient was relieved of asthma, but it is impossible to state what treatment relieved, since she omitted both wheat and egg from the diet, and at the same time was treated with horse dandruff protein. It is not fair to condemn the skin test in the two cases which were positive with only wheat leucosin or in the two positive to corn alone, since these four patients might perfectly well be sensitive to these proteins but never eat them in sufficient quantities or sufficiently often to cause trouble. In the three patients, however, who gave positive skin tests with several of the cereals, it must be admitted that at the present time the cereals played little or no part in the cause of their asthma and in that respect the positive skin tests were misleading; still, they should be considered as danger signals and not disregarded. This point is well illustrated by a patient who gave a positive skin test with corn and oats, but these proteins did not cause asthma at that time, and asthma was relieved by vaccines; later, however, asthma returned and resisted vaccine treatment. The patient was at this time eating a great deal of oats and corn in "war bread," and omission of these from the diet this time relieved the asthma.

Thirty-three patients (8.25 per cent. of the total, or 17 per cent. of the total sensitive patients) gave positive skin tests to food proteins other than the cereals. Of this number, fifteen patients gave a positive skin test with egg, seven with potato, seven with fish, five with casein, two with chicken and two with beef. Occasionally a patient would be found sensitive to strawberry, spinach, peach, etc., but as these proteins were not tested routinely, it is impossible to show the relative frequency of sensitization to them. Since in these patients these foods proved to be a cause of asthma, however, it may be said that probably any food protein may cause asthma.

Since most of the patients in this group were sensitive to other food proteins as well as egg, potato, fish and casein, it is often hard to determine just what part these foods, which are not being eaten daily, do actually play in the cause of asthma. Furthermore, the fact that many of these patients have eczema as well as asthma complicates the

interpretation of the positive skin test, but it does not detract from the value of the test.

Of the fifteen patients who were sensitive to egg protein, two were relieved of asthma by the omission of egg from the diet; three others had avoided eggs since early childhood because eggs were distasteful; two patients had eczema, three were treated with and relieved by horse dandruff protein in conjunction with the omission of eggs from the diet, and the remaining five patients were also sensitive to other foods as well as egg and the omission of all of these foods relieved asthma. Therefore, it is impossible to say in just how many patients egg protein was the cause of asthma, but there is sufficient evidence to show that all of these patients were sensitive to egg, as was shown by the positive skin tests.

Of the seven patients who gave a positive skin test with potato, three were relieved of asthma by the omission of potato from the diet, and two others who were also sensitive to other foods, were relieved by the omission of all of these foods from the diet. Of the five patients who were sensitive to casein, two were relieved by the omission of casein from the diet and one always had urticaria after the ingestion of milk. There were two patients who gave positive skin tests with both potato and casein in whom neither of these proteins seemed to play a part in the cause of asthma. These same two patients also gave positive skin tests with the cereals (see the foregoing), and with fish (see following), and in neither did these seem to be a cause of asthma. Therefore, it seems fairer to conclude that these two patients had a hyperirritable skin rather than to condemn the skin test.

Of the seven patients who gave positive skin tests with fish protein, in four fish definitely caused asthma, in one fish caused urticaria and in the other two patients there was no evidence for a positive skin test with the exception that the patient's skin was irritable (see the foregoing). The types of fish to which the patients were sensitive were lobster, salmon, mackerel, cod, oyster and haddock. Of the two patients who were sensitive to beef, one definitely had asthma when beef was eaten and the other patient thought that she was worse when she ate beef. Both of the patients who were sensitive to chicken meat, had asthma after eating chicken and only after eating it.

The relationship between the age of onset of asthma and sensitization to these food proteins shows that the younger the patient is when asthma begins the more liable is he to be sensitive to food proteins. Nine of the fifteen patients who were sensitive to egg protein, had had asthma since infancy, two others since the age of 2, and two others since the age of 3 and 4, respectively. Among the seven patients who were sensitive to potato, two had had asthma since 1 year of age, and one since 2 years of age. Among the five patients who were sensitive

to casein, two had had asthma since 1 year of age and one since 2 years of age. The remaining cases in this group began to have asthma during childhood, with the exception of the two patients who had an irritable skin, and these two were adults. With the exception of bakers, the majority of those who were sensitive to the cereals began to have asthma in early childhood.

It is noted that the treatment of those patients who were sensitized to food proteins differs from the treatment of those who were sensitive to animal hair proteins. In the latter cases desensitization was readily accomplished by the subcutaneous injection of the proteins. Those patients who were only slightly sensitive to the food proteins were satisfactorily desensitized by the subcutaneous method, but this treatment was not satisfactory in those patients who were very sensitive to the food proteins. With two patients attempts at desensitization by feeding the protein in small, gradually increasing amounts were unsuccessful because the patients (in spite of the fact that they were chosen from a large group as the most apt to follow explicit directions) did not cooperate as they should. Therefore, with the food proteins, treatment has consisted of omission of the offending food from the diet, and this has been very successful. It is not, however, the easiest matter absolutely to restrict the eating of the cereals and egg since they enter into the composition of practically all pastry and gravies, and for this reason the attention of the patient must be called to their extensive use. Another source of error as regards the cereal flours is the contamination of one grain with occasional kernels of the other grains before they are ground into flours. We have overcome this difficulty by having the patient purchase the whole grain, pick it over carefully in order to reject the few kernels which that patient should not eat, then the patient grinds the grain in his own coffee mill at home. The purchase of so-called pure flours has not been satisfactory, as many times these flours have contained ingredients which we desired to avoid; this has been especially true of rye and rice flour. Attention should be called to the fact that patients who are sensitive to corn, oat, rye and barley proteins were, before the war, eating these too infrequently and too sparingly, as a rule, to cause trouble; but since the war began these flours are being eaten so extensively that they are frequently the cause of symptoms in such cases. The duration of freedom from symptoms in these food cases depends on the length of time they are omitted from the diet. As long as they are omitted, just so long will the patient remain free from symptoms. It remains to be seen how long total abstinence is necessary to effect desensitizations. It would seem, however, that total abstinence will eventually effect desensitization, since all of those who have studied infants and chil-

dren have found sensitization to egg protein in a high percentage of cases, whereas in this series of 400 cases, the majority of whom were young adults or older, there were only fifteen egg cases, or a percentage of only 3.75 per cent. It would seem plausible that many more of our patients probably, earlier in life, had been sensitive to egg and later on became desensitized; the history of distaste for certain foods is frequent and probably this is nature's way of protecting against them.

CONCLUSIONS

Of the forty-eight patients who were sensitive to and treated with horse dandruff proteins, 63 per cent. were relieved of asthma, 10 per cent. have had too little treatment to warrant a prognosis, and 20 per cent. were relieved by vaccines or by omitting foods to which they were sensitive; in the remaining 7 per cent. of this group treatment was a failure.

Of the four patients who were sensitive to and treated with cat hair protein, three were relieved of asthma, and the other patient, who was equally sensitive to the horse dandruff proteins, was relieved by treatment with them.

Of the thirty patients who were sensitive to the cereal grains, 74 per cent. were relieved by the omission of these from the diet, and 7 per cent. were relieved by vaccines; of the 26 per cent. who were not relieved by the omission of cereals from the diet, in 16 per cent. there was no evidence that cereals played any part in the cause of asthma, but the presence of eczema may account for these positive skin tests.

Of the thirty-three patients who gave positive skin tests to other foods, 50 per cent. were relieved by the omission of these from the diet, 30 per cent. more were relieved of asthma, but as the latter were also sensitive to other proteins which were also omitted from the diet at the same time, it is difficult to give credit to any special protein. The remaining 20 per cent. were not relieved of asthma, but the presence of eczema and urticaria and an acquired distaste for certain foods probably explains the idiosyncrasy.

Therefore, of the total number of 100 sensitive individual patients who were treated as indicated by the positive skin tests, in 75 per cent. there was relief from asthma, in 14 per cent., although there was no relief from asthma, there was a definite idiosyncrasy substantiating the positive skin test; but in 11 per cent. the positive skin test had no apparent bearing on the patient's condition, although in only half of these, or 5 per cent., was there evidence that the skin test gave a false result. Since the 11 per cent. includes 7 per cent. who were relieved by vaccines, a total of 82 per cent. of the sensitive patients were relieved from asthma.

THE INFLUENCE OF ACID PHOSPHATE ON THE ELIMINATION OF AMMONIA IN THE URINE*

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In the course of nephritis severe acidosis may develop. Although all the usual evidences of acidosis are present, there is no increase in the ammonia of the urine. To this extent it differs from the acidosis resulting from the ingestion of strong mineral acids or from the overproduction of organic acids in the body such as beta-oxybutyric and aceto-acetic acids. Henderson and Palmer[1] have pointed out that the titratable acidity of the urine in the acidosis of nephritis may be normal in amount though the total excretion of acid is low, due to "a never failing deficit in urinary ammonia." These observations would indicate that the acid responsible for the disturbance of the acid base equilibrium in nephritis is distinctly different in character from those acids causing acidosis in other conditions.

We have previously demonstrated[2] that an accumulation of inorganic phosphate occurs in the blood plasma of nephritics coincident with the development of acidosis. It is the failure of the kidney to excrete acid phosphate which, we believe, results in the production of acidosis.

Spiro,[3] Austin and Jones[4] and others have shown that acidosis may be caused by the administration of acid phosphate. It has not been shown why, in the presence of an undoubted acidosis, there is no increase in the urinary ammonia. It has seemed logical, therefore, to give to normal people acid phosphate and hydrochloric acid in equimolecular amounts to determine if there is a different influence on ammonia production brought about by the ingestion of these two acids.

The subjects for the experiment were four normal men, laboratory workers. Each was on his usual diet during the course of the experiments. The food intake was not controlled further than the avoidance of dietary excesses. The total nitrogen excretion in the urine from day to day indicated that the protein intake was fairly constant. The

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1. Palmer, W. W., and Henderson, L. J.: Jour. Biol. Chem., 1915, **21,** 37. THE ARCHIVES INT. MED., 1915, **16,** 109.
2. Marriott, W. McK., and Howland, J.: THE ARCHIVES INT. MED., 1916, **18,** 708.
3. Spiro: Beitr. z. chem. Phys. u. Path., 1902, **1,** 269.
4. Austin and Jones: Am. Jour. Med. Sc., 1917, **153,** 81.

urine was collected for twenty-four-hour periods ending at 7 a. m., preserved with thymol and chloroform and kept at a low temperature.

The hydrogen-ion concentration of the urine was determined by the method of Henderson and Palmer;[5] titratable acidity by the method of Henderson and Adler;[6] ammonia by the microchemical method of Folin and McCallum.[7] All the above determinations were made within a few hours after the twenty-four-hour samples were complete. Total nitrogen was determined by the Kjeldahl method and phosphates by uranium titration.

The experiment continued over twelve days. There was a preliminary period of three days during which each person remained on his normal diet. During the fourth day each subject drank 500 c.c. of decinormal hydrochloric acid. The acid was all taken during the first twelve hours of the twenty-four-hour period. Following this there was another "normal" day. Then each subject took the equivalent of 500 c.c. of decinormal acid sodium phosphate (NaH_2PO_4); that is to say, the amount of acid sodium phosphate taken was such that when in solution 500 c.c. of decinormal sodium hydroxid (NaOH) were required to bring the reaction to that of the body; that is, a hydrogen-ion concentration of $10^{-7.4}$. The actual amount of acid sodium phosphate was 36.5 gm.

The following day 1,500 c.c. of decinormal acid sodium phosphate (109.5 gm.) were taken by each subject. Two "normal" days followed and then each subject took a solution of sodium phosphate having a hydrogen-ion concentration of $10^{-7.4}$—that is the reaction of the body—and containing the same amount of phosphate (PO_4) as the 500 c.c. of decinormal acid phosphate. The following day 1,500 c.c. of decinormal neutral phospate were taken. A subsequent "normal" day completed the experiment.

The results obtained by urinary analysis appear in the accompanying table.

Average values for some of the important factors are plotted graphically in the accompanying chart.

From the results it appears that hydrochloric acid administration increases distinctly the ammonia coefficient in the urine; the titratable acid increases in about the same proportion, so that the A/NH_3[8] ratio remains essentially unchanged. That this would occur has already been demonstrated many times by others. The observation was

5. Henderson and Palmer: Jour. Biol. Chem., 1913, **13,** 393.
6. Henderson and Adler: Proc. Soc. Biol. Chem., 1908, p. 38.
7. Folin and McCallum: Jour. Biol. Chem., 1912, **11,** 523.
8. A represents the total titratable acid for twenty-four hours, and NH_3 the total urinary ammonia, each expressed in cubic centimeters of decinormal solution.

RESULTS OF URINALYSIS IN AUTHORS' EXPERIMENTS

Subject	Day	Vol.	T.N.*	P.	pH	A	NH_3	$\frac{A}{NH_3}$	
A	1	2,060	12.6	0.83	5.95	260	360	0.72	
	2	2,260	11.3	0.80	6.20	228	363	0.63	
	3	1,560	13.0	0.92	5.70	316	312	1.00	
	4	3,130	12.6	1.10	5.60	377	448	0.83	500 c.c. decinormal hydrochloric acid
	5	2,620	13.5	0.82	6.0	257	350	0.73	
	6	2,950	11.2	1.45	6.2	348	319	1.09	500 c.c. decinormal acid phosphate
	7	2,715	11.6	2.71	5.9	665	360	1.85	1,500 c.c. decinormal acid phosphate
	8	2,440	10.9	1.66	5.8	444	312	1.42	
	9†								
	10	3,000	9.3	1.53	6.85	210	241	0.87	500 c.c. decinormal neutral phosphate
	11	2,200	8.8	1.85	6.8	150	139	1.08	1,500 c.c. decinormal neutral phosphate
	12	2,320	12.2	1.46	6.7	270	271	1.00	
B	1	1,470	12.3	0.85	6.8	120	280	0.43	
	2	1,320	13.4	0.96	6.5	196	292	0.67	
	3	1,050	13.6	0.98	5.8	306	382	0.80	
	4	1,720	12.0	0.87	5.5	349	504	0.69	500 c.c. decinormal hydrochloric acid
	5	1,040	12.3	0.88	6.2	214	376	0.57	
	6	1,428	14.0	1.84	6.45	366	360	1.03	500 c.c. decinormal acid phosphate
	7	1,640	13.2	4.14	6.1	860	356	2.42	1,500 c.c. decinormal acid phosphate
	8	1,160	11.7	2.02	5.9	480	351	1.37	
	9	1,255	10.5	1.20	6.5	252	286	0.88	
	10	1,120	12.0	2.18	6.7	282	257	1.10	500 c.c. decinormal neutral phosphate
	11	1,575	13.1	3.56	6.85	144	197	0.73	1,500 c.c. decinormal neutral phosphate
	12	1,260	12.0	1.82	6.80	220	255	0.86	
C	1	1,440	16.8	1.19	6.3	300	400	0.75	
	2	1,310	15.8	1.42	5.7	420	460	0.91	
	3	1,210	16.2	1.43	5.65	456	449	1.03	
	4	1,270	16.9	1.30	5.5	496	566	0.87	500 c.c. decinormal hydrochloric acid
	5	1,215	15.6	1.23	5.5	440	560	0.79	
	6	1,795	21.2	2.60	5.7	694	585	1.18	500 c.c. decinormal acid phosphate
	7	3,920	16.4	5.40	5.5	1,400	550	2.54	1,500 c.c. decinormal acid phosphate
	8	1,230	12.8	2.24	5.65	612	570	1.07	
	9	1,225	14.2	1.30	5.75	370	444	0.83	
	10	1,700	12.3	2.52	6.2	556	376	1.48	500 c.c. decinormal neutral phosphate
	11	2,000	17.1	5.18	6.8	576	285	2.02	1,500 c.c. decinormal neutral phosphate
	12	2,360	15.3	2.05	6.7	270	374	1.00	

* T.N. = total nitrogen, grams per day; P. = total inorganic phosphorus, grams per day; pH = hydrogen-ion concentration of urine expressed by the negative logarithm; A = titrable acid in terms of cubic centimeters of decinormal solution; NH_3 = ammonia expressed in like manner.

† Urine lost.

RESULTS OF URINALYSIS IN AUTHORS' EXPERIMENTS—(*Continued*)

Subject	Day	Vol.	T.N.*	P.	pH	A	NH_3	$\frac{A}{NH_3}$	
D	1	1,300	12.4	1.06	5.5	370	485	0.76	
	2	3,510	12.2	1.04	6.3	272	430	0.63	
	3	1,192	11.9	0.97	6.4	232	379	0.61	
	4	1,330	12.4	0.93	5.5	394	596	0.66	500 c.c. decinormal hydrochloric acid
	5	760	9.5	1.00	5.55	330	460	0.72	
	6	1,375	12.4	2.04	5.8	494	423	1.16	500 c.c. decinormal acid phosphate
	7	1,340	12.0	3.40	5.8	800	490	1.63	1,500 c.c. decinormal acid phosphate
	8	1,450	14.2	1.68	6.0	453	497	0.91	
	9	910	10.7	0.82	6.3	196	344	0.57	
	10	810	12.3	1.88	6.2	430	402	1.07	500 c.c. decinormal neutral phosphate
	11	1,005	12.5	3.98	6.7	420	330	1.27	1,500 c.c. decinormal neutral phosphate
	12	1,495	10.2	1.90	6.6	322	376	0.86	
Averages	1	1,570	13.5	0.98	6.15	262	381	0.68	
	2	2,100	13.2	1.06	6.4	279	386	0.71	
	3	1,250	13.7	1.08	5.9	328	380	0.86	
	4	1,800	13.5	1.05	5.5	404	529	0.76	500 c.c. decinormal hydrochloric acid
	5	1,410	12.7	0.98	5.8	310	437	0.71	
	6	1,800	14.7	1.98	6.05	476	422	1.13	500 c.c. decinormal acid phosphate
	7	2,400	13.3	3.91	5.8	956	439	2.17	1,500 c.c. decinormal acid phosphate
	8	1,570	12.4	1.88	5.85	512	433	1.19	
	9	1,130	11.8	1.11	6.1	273	358	0.76	
	10	1,060	11.5	2.03	6.5	367	319	1.14	500 c.c. decinormal neutral phosphate
	11	1,690	12.9	3.65	6.8	323	238	1.36	1,500 c.c. decinormal neutral phosphate
	12	1,860	12.4	1.81	6.7	295	319	0.93	

repeated by us for the purpose of comparison with the effect of acid phosphate on the same individuals.

The administration of acid phosphate equivalent in titratable value to the hydrochloric acid, that is, 500 c.c. of decinormal solution, led to absolutely no increase in ammonia excretion and even three times this amount (1,500 c.c. of decinormal solution) also failed to increase the excretion of ammonia. There was, however, a great increase in the titratable acid of the urine, so that the A/NH_3 ratio increased greatly, reaching a point corresponding to that observed by Henderson and Palmer[9] in severe nephritic acidosis. This difference in behavior of the phosphoric and the hydrochloric acid may be due to a difference in "strength." Equimolecular quantities of the "weak" acid phosphate

9. Jour. Biol. Chem., 1915, **21**, 37.

and the "strong" hydrochloric acid should cause an equal increase in the titratable acidity of the urine, whereas a "weak" acid added to blood would neutralize bicarbonate, but would not cause as great a change in reaction as would a "strong" acid. It is this difference that may account for the failure of the weak acid phosphate to call forth ammonia.

Since the administration of 500 c.c. of decinormal acid phosphate is essentially the same (except for inert sodium chlorid) as the administration of an equivalent amount of neutral phosphate to which 500 c.c. of decinormal hydrochloric acid have been added, it would

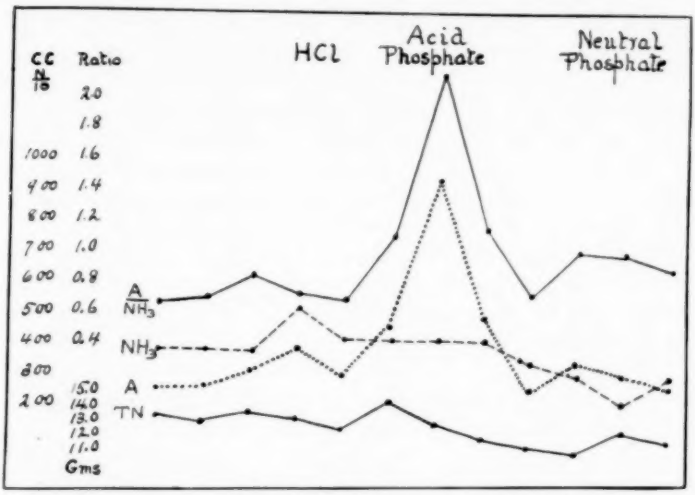

Chart showing average values of some important factors.

appear that the presence of phosphate in the body actually inhibits the formation of ammonia, since hydrochloric acid alone led to a great increase. If this were true the administration of neutral phosphate, that is, phosphate at exactly the reaction of the body, should decrease the ammonia excretion of the normal subject. Our results show this to be the case. Neutral phosphate which calls for no defense of the body against either acid or alkali leads to a decrease in the excretion of ammonia, as may be seen from the table and chart. The A/NH_3 ratio becomes greater than that ordinarily seen in normal individuals.

In the presence in quantity of phosphates in the blood the addition of a strong acid would convert a portion of the phosphate into acid phosphate and this would have less effect on the hydrogen-ion concentration, and for this reason would be expected to call forth the production of less ammonia than would the strong acid in the absence

of phosphate "buffer." This may well be the explanation for the actual diminution of ammonia excretion which we have observed following the ingestion of neutral phosphate.

We have previously demonstrated the retention of inorganic phosphates in the blood of nephritics with acidosis and have expressed the opinion that the acidosis depends on the retention of acid phosphate. The experiments reported in this paper show that the presence of acid phosphate in the body, even in the absence of renal disease, gives rise to the excretion of urine of a character such as has been previously observed exclusively in nephritic acidosis. These results, in our opinion, give additional confirmation to the view that the acidosis occurring in the course of nephritis is due to the retention of acid phosphate.

BOTULISM

A FURTHER REPORT OF CASES OCCURRING IN THE PACIFIC COAST STATES *

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In a previous report[1] it was shown that prior to September, 1917, there had been twenty-two recorded outbreaks of botulism in the United States, in which eighty-one persons were poisoned and fifty-five died. In this collection of cases one important outbreak had been overlooked. In January, 1912, Dr. A. R. McCracken[2] of Seattle reported a series of six cases of poisoning by home-canned asparagus, in which three of the patients died. In all, therefore, there have been at least twenty-three recorded outbreaks of botulism in this country, of which nineteen occurred in the Pacific Coast States. The mortality of these recorded cases was 66.6 per cent.

In addition to the outbreaks in which human beings were affected there were also at least six instances in which domestic fowl were poisoned and showed symptoms which were identical with those produced experimentally by feeding with the toxin of *Bacillus botulinus*.

ETIOLOGIC FACTORS

It is an important fact that, of the twenty-five instances of poisoning of human beings or domestic fowl in which the source of the poisoning was determined, seventeen were shown to have been caused by the ingestion of home-canned vegetables or fruits, and in three instances it was established that the poisoning was due to the toxin of *B. botulinus*, by the recovery of *B. botulinus* from portions of the discarded food.

Since September, 1917, there have been at least ten more outbreaks of botulism affecting human beings and four affecting domestic fowl or animals, and of these fourteen outbreaks, thirteen have been shown to be due to the ingestion of home-canned vegetables or fruits. Seven of the outbreaks affecting human beings and all of those affecting domestic animals and fowl occurred in the Pacific Coast States, and

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* Aided by a grant from the California State Council of Defense.

1. Dickson, E. C.: Botulism: The Danger of Poisoning from Vegetables Canned by the Cold-Pack Method, Jour. Am. Med. Assn., 1917, **69**, 966.
2. McCracken, A. R.: Botulism, Leucocyte, 1912, **19**, 80.

from remnants of the home-canned products which caused three of them, *B. botulinus* was recovered. One of the remaining outbreaks occurred in Fallon, Nev., one in Decatur, Ind., and one in Newark, N. J. I have been informed that *B. botulinus* was recovered from the discarded food in two of these. It is probable that the complete report of these outbreaks will be recorded by the physicians who cared for the patients.

DANGER IN HOME CANNING OF PERISHABLE FOODS

The increase in the number of outbreaks of botulism in this country bears a very interesting relationship to the marked increase in the practice of home-canning of perishable foods which has taken place during the past few years. The home-canning of vegetables is a development of comparatively recent years, but on account of the increased cost of food products since the beginning of the war, and especially since the inauguration of the program for the conservation of foods during the past year, the amount of vegetables which are canned at home has been tremendously increased. Coincidently with the increase in the amount of home-canning of vegetables as well as of fruits there has been a marked increase in the number of outbreaks of botulism in the United States, and it is extremely interesting that not only is there an increase in the number of instances of poisoning of human beings, but there are also more frequent occurrences of poisoning of domestic fowl and animals by feeding spoiled home-canned products (Table 1).

TABLE 1.—SHOWING THE OCCURRENCE OF RECORDED OUTBREAKS OF BOTULISM DURING THE PAST NINETEEN YEARS, AND THE IMPORTANCE OF HOME-CANNED PRODUCTS AS THE CAUSE OF THE POISONING

Period From To	Interval	Number of Outbreaks		Source of Poisoning			
				Home-canned		Food of Animal Origin	Unknown
		Human	Domestic*	Vegetable	Fruit		
1899 - 1903	5 years	2	.....	...	...	2	...
1904 - 1908	5 years	1	Fowl 1	1	...	1	...
1909 - 1913	5 years	10	.....	8†	1	3	1
1914 - Sept. 1917	3¾ years	10	Fowl 5	10	1	1	3
Oct. 1917 - Mar. 1918	½ year	10	Fowl 3 Hog 1	10	3	...	1

* The outbreaks listed under "Domestic" were instances in which only fowl or animals were affected and do not include those in which human beings and fowl or animals were coincidently poisoned.

† One outbreak was caused by commercially-canned vegetables.

A. REPORT OF OUTBREAKS IN WHICH HUMAN BEINGS WERE POISONED *

OUTBREAK 8 (three cases).—On Sunday, Nov. 25, 1917, Mrs. E. of Seattle, opened a jar of home-canned asparagus and cooked half of the contents. None of the persons who ate the cooked asparagus suffered any ill effects. On the following evening she "warmed up" the remainder of the asparagus from the jar, by placing it for a few minutes in warm but not boiling water. Her husband stated that this asparagus did not taste very good, but he ate it all. On Tuesday afternoon Mr. E. complained of disturbance of vision, was nauseated and vomited. On Wednesday morning he was very weak, vomited again after taking food, and had severe diarrhea. The diarrhea continued during the day and following night, and during the night the patient complained of cramps in the legs. There was no abdominal pain during this time, and no disturbance of sensation. During Wednesday afternoon he began to have difficulty in talking. On Thursday Mr. E. was unable to sit up because of weakness, and he complained that he could not hold up his head. He was unable to speak intelligibly, and he complained of dryness in the mouth and pharynx. During the afternoon he began to have difficulty in swallowing, and by evening "all the water returned through his nose." He had much difficulty in clearing thick, tenacious mucus from the pharynx and had severe strangling spells when he attempted to swallow. There was no disturbance of mentality, no pain except the cramps in the legs, and no fever. He was found dead in bed early Friday morning, about two hours after he had succeeded in swallowing a small amount of milk.

On Thursday, November 29, another jar of the same lot of asparagus was opened and was served cold as salad at the Thanksgiving dinner. Two persons partook of the salad and both developed symptoms of poisoning and died. One patient was seen by Dr. O. F. Lamson, who placed his records at my disposal. The clinical course of Dr. Lamson's case was practically identical with that of the case which has been described, although there was much more severe strangling when the patient attempted to swallow. The temperature varied from 97 to 98.8 F., and the pulse from 92 to 128 per minute. The patient died on the fourth day after eating the asparagus salad.

Through the courtesy of Dr. Lamson and Coroner Tiffin of Seattle, I was permitted to do partial necropsy on the bodies of two of the victims, although a coroner's necropsy had been previously performed in each case, and both bodies had been embalmed. There was moderate congestion of the meninges and of the abdominal and thoracic viscera in each case, and apparent bronchopneumonia in one. No macroscopic hemorrhages were seen. On microscopic examination a few typical thrombi were found in each case, in one occurring in the larger meningeal arteries, and in the other, occurring in the lungs. No disintegration of the Nissl granules was detected.

The remnants of the salad which had been served on Thanksgiving day were fed to the chickens, and all the chickens developed typical symptoms of limber-neck, and died. Bacteriologic examination was made of the contents of the crops and gizzards of ten of the chickens, and from six of them a virulent strain of *B. botulinus* was isolated. This strain is labeled Strain 7 of my series.

The asparagus was canned according to the directions published on page 19 of the pamphlet issued by the Kerr Glass Manufacturing Company, with the exception that it was not parboiled or blanched before it was packed in the

* In detailing the case histories only those facts are described which are essential for establishing the diagnosis. For a more complete discussion of symptomatology and pathology refer to Dickson, E. C.: Botulism: A Clinical and Experimental Study. Monograph of the Rockefeller Institute for Medical Research, No. 8, 1918, in which Outbreaks 1 to 7 of my series are described.

jars. The material was purchased in the city market, washed in cold water, packed into 1-pint and 1-quart Mason jars which had been boiled, and covered with cold water to completely fill the jars. One-half teaspoonful of salt was added to each jar and the covers were loosely applied. The jars were immersed to the neck in a wash-boiler which had a tightly fitted cover, and were allowed to remain for three hours after the water began to boil actively. On removal from the boiler, the jars were tightly sealed and placed in a dark closet.

Outbreak 9 (one case).—On Wednesday, Dec. 5, 1917, Miss B. of Ontario, Ore., opened a jar of home-canned string beans and tasted the contents to determine whether they were good. She decided that they were "not exactly right" and discarded them. On the following day she complained of blurred and double vision and difficulty in articulation, and consulted Dr. Rollo A. Payne of Ontario, Ore., who sent me the records of the case.

When Dr. Payne first saw the patient there was bilateral blepharoptosis, dilatation of the pupils and difficulty in articulation. There had been no nausea or vomiting, no pain and no diarrhea. On the following day the blepharoptosis was more marked, speech was unintelligible and the patient was very restless, being compelled to struggle for breath. There was great difficulty in swallowing. Examination of the urine showed nothing abnormal, and the blood pressure was 142 mm. (systolic). Miss B became rapidly worse and died about fifty-two hours after tasting the beans. Dr. Payne stated that the symptoms were those of a bulbar paralysis which "interfered more with the respiratory and throat muscles than with other groups." Death was apparently from respiratory failure.

The discarded beans were thrown to the chickens, and thirty-nine of them died of limber-neck within two or three days after eating them.

It was not possible to learn the details of the method which was followed in canning the beans.

Outbreak 10 (two cases).—On Friday, Jan. 11, 1918, Dr. P. M. Savage of San Bernardino, Calif., was called to see Mrs. J. who gave the following history:

On Thursday afternoon she had noticed that she "saw double," but was otherwise quite well. On Friday morning she was very weak, and was scarcely able to walk; in fact, she had fallen three times while preparing breakfast. Just before Dr. Savage was called, the patient had staggered to a neighbor's house for help, but collapsed before reaching the door. When first seen she was seated in a chair, without apparent pain, and apparently without any disturbance of mentality. She complained of weakness, double vision and photophobia. There was bilateral blepharoptosis, dilatation of the pupils and loss of reflex to accommodation, though not to light. Articulation was very deliberate and indistinct. When the patient stood she became dizzy and there was incoordination of muscular movements. The skeletal reflexes were intact and there was no appreciable disturbance of sensation. The temperature was 99.5 F. and the pulse rate was 100.

On Saturday morning there was still photophobia and double vision, and the patient complained of great fatigue. There was difficulty in swallowing and the patient had severe strangling spells when she attempted to swallow. During the morning articulation was distinct, although husky, but by evening speech was unintelligible. During the day she became rapidly worse, swallowing became more difficult and strangling spells more frequent. There was much distress from the accumulation of thick, tenacious mucus in the pharynx. There was persistent constipation, but urination was not disturbed. The temperature varied from 97.8 to 99.5 F., and the pulse rate from 80 to 100. The patient died early Sunday morning.

Meantime on Thursday night, Miss H., a blind woman to whom Mrs. J. was companion, developed severe cramps in the abdomen with nausea, vomiting and diarrhea. She became extremely nervous, almost hysterical, and on Friday was much fatigued. During Friday night she had difficulty in swallow-

ing and by Saturday morning she strangled when she attempted to swallow. She coughed a great deal, but was unable to raise the thick, tenacious mucus from the pharynx. Articulation became difficult and speech was indistinct. There was persistent constipation after the initial diarrhea, and, except for the initial cramps, there was no pain. On account of the blindness no disturbance of vision was noted. The patient died Sunday night.

Necropsy was not obtained in either case. There was a history of both persons having eaten home-canned apricots which did not taste just right, but unfortunately the remnants of the apricots had been discarded. There was no record of the method used in canning the apricots or of the exact time at which the apricots were eaten.

Outbreak 11 (eight cases).—On Sunday, Jan. 27, 1918, a party consisting of nine persons, five adults and four children, had supper together near Madera, Calif. The supper consisted of fresh pork, brown beans, bread, butter, milk and home-canned apricots. It was noted that the apricots had a peculiar taste, but eight of the party ate some of them. The only member of the party who escaped illness was the one who did not eat any of the apricots.

On Tuesday morning, January 29, three of the children, aged 3½, 5 and 14 years, respectively, complained of seeing double, and three of the adults complained of dizziness. The three adults also developed diplopia during the day. The fourth adult first showed symptoms of illness Tuesday night, and the smallest child, aged 13 months, became ill Wednesday evening. One of the children died Wednesday morning, January 30, two Wednesday evening and one Friday morning. Two of the adults died during the night of Thursday and the remaining two have apparently recovered after a prolonged illness.

Drs. D. H. Ransom and St. J. Hely of Madera were called to care for the patients and it is to them that I am indebted for permission to study the cases, to perform necropsy in one case and to obtain various materials for bacteriologic examination.

The symptoms of all the patients were practically identical except in degree of severity. In all there were dizziness, weakness and incoordination of muscular movement, early disturbance of vision with blepharoptosis, mydriasis and diplopia, difficulty in swallowing and talking and strangling spells induced by attempts to raise thick mucus from the pharynx or to swallow. In one case, one of the patients who recovered, there was initial diarrhea and vomiting which occurred from twelve to fifteen hours before the onset of the eye symptoms, but in none of the other cases were there acute gastro-intestinal manifestations. In all the cases there was persistent constipation. The following case reports are very typical.

THREE CASE REPORTS IN DETAIL

Case 1.—*History.*—F. M., aged about 60, had supper with the rest of the family on Sunday evening and ate some of the apricots. He worked all day Monday, although he "felt a little out of sorts," and slept well Monday night. On Tuesday morning he was very dizzy, and, later in the day, began to see double. There was free movement of the bowels after magnesium sulphate. He again slept well Tuesday night but on Wednesday morning was very weak and uncertain in his movements, although he remained up all day. He still complained of double vision and "blurring." On Thursday morning he was so weak that he was unable to dress. There was some vertigo. For the first time the patient complained of dryness of the mouth and pharynx, and during the day he began to have difficulty in swallowing and talking. Toward evening there was much difficulty in clearing thick mucus from the pharynx, and the patient began to have severe strangling spells when he attempted to swallow. He was very restless Thursday night and slept little, although there was no pain. On Friday morning he complained of being very hungry but said he was afraid to try to swallow. He complained

of being very weak, but was able to move himself in bed with little difficulty. There had been no bowel movement for three days.

Bedside Notes.—Physical examination was made by me on Friday about 10 a. m. The patient was lying comfortably in bed, apparently without pain. The temperature was 96.4 F., the pulse rate 72, and the rate of respiration 16. Respiration was not labored. Articulation was very much impaired; it was almost impossible to understand what was said, and the patient became quite irritable and stubborn when asked to repeat. He was able to raise himself in bed without difficulty and there was no apparent weakness of the muscles of the neck.

There was bilateral blepharoptosis, the pupils were dilated and reacted sluggishly to light, and the patient complained of photophobia and diplopia. There was no nystagmus. The mucous membrane of the mouth and pharynx was very dry and the tongue was swollen, heavily coated and fissured. The breath was very offensive.

Examination of the chest revealed nothing abnormal in the lungs. The area of cardiac dulness was slightly increased but the heart sounds were clear and the heart rate was not rapid. The blood pressure was 140 mm. systolic and 90 mm. diastolic (Tycos). The abdomen was relaxed and soft, there were no areas of tenderness, and no abnormal masses were felt. The skin was everywhere dry and somewhat atrophic.

Sensation was apparently unimpaired, mentality was clear, and the knee-jerks, plantar reflexes and biceps reflexes were normal.

Laboratory Examination.—The red blood corpuscles numbered 5,300,000 and the leukocytes 16,000, of which 88 per cent. were polymorphonuclear neutrophils, 9 per cent. were lymphocytes, 2 per cent. were mononuclears and 1 per cent. eosinophils.

The urine contained neither albumin nor casts, and microscopic examination of the sediment showed no casts, red blood cells, or other abnormal constituents.

Treatment.—On Friday afternoon feeding and administration of magnesium sulphate by stomach tube was commenced, and was continued until the patient was again able to swallow. Between Friday at midnight and Monday noon about 85 c.c. of immune goat serum were administered subcutaneously. (One c.c. of the serum was sufficient to neutralize approximately 3,000 minimum lethal doses of botulism toxin for a guinea-pig.) Supporting treatment was given throughout and a digitalis preparation and whisky were given when indicated. The necessary fluid was given by Murphy drip when the patient was unable to swallow.

Clinical Course.—For several days the patient appeared to be very ill, was unable to swallow, talk or control muscular movements, and was very weak. He was very restless and slept little. He was frequently irritable, but was always mentally clear. The temperature varied from 97.6 to 101 F. (by rectum) and the pulse rate was usually between 85 to 95 per minute.

By February 6 there began to be some signs of improvement. The patient was not so restless, he slept better, and at times was able to swallow small amounts of fluids. On February 10 he looked very much better and was able to talk more intelligibly. He stated that there had never been any pain except at the site of inoculation. The pupils were still dilated and still reacted sluggishly to light, but there was no diplopia. Bilateral ptosis persisted. The tongue was coated and very dry and fissured, but there was no longer an accumulation of mucus in the pharynx. Muscular coordination was improved, and the skeletal reflexes were normal.

Results.—On March 10, six weeks after the patient had eaten the apricots, he was able to be up, to walk without staggering and "to swallow fairly well." There was no ptosis, no dilatation of the pupils and no disturbance of vision. The voice was still husky, especially after a prolonged conversation, but articu-

lation was distinct. The patient became dizzy if he attempted to move quickly, but stated that he was rapidly growing stronger and more sure of himself. There was no evidence of any persisting paralysis.

CASE 2.—*History.*—C. M., aged 24, ate nothing but apricots, bread and butter for supper Sunday evening. He felt perfectly well on Monday, but on Tuesday afternoon he vomited and had diarrhea. On Wednesday he began to have double vision and dizziness, and he complained that when he tried to walk he staggered as if he were drunk. He was very restless and did not sleep well Wednesday night. On Thursday he was unable to leave his bed, and, although he was very hungry, he was unable to swallow any food. It was noted that enunciation was very difficult and indistinct.

Examination.—When seen by me on Friday, there was bilateral ptosis and some photophobia but the pupils were not dilated, and they reacted fairly actively to light stimulation. The skin was dry, the tongue heavily coated and the mucous membrane of the mouth and pharynx parched. There was no congestion of the pharynx. There were no signs of impairment in the lungs and the heart was apparently normal. There was nothing abnormal in the skeletal reflexes.

There was no demonstrable disturbance of peripheral sensation, and the patient was apparently quite clear mentally, although he became irritable when he could not make himself understood. Speech at this time was almost unintelligible.

The blood pressure was 135 mm. systolic and 90 mm. diastolic (Tycos), and the urine showed no albumin or casts. The red blood corpuscles numbered 5,600,000 and the leukocytes 19,000, of which 80 per cent. were polymorphonuclear neutrophils, 18 per cent. were lymphocytes and 2 per cent. were eosinophils.

Clinical Course.—At first it appeared as if the patient was much less severely poisoned than his father, but gradually he became much worse, due chiefly to the fact that he had a great deal of cough and many severe strangling spells. The temperature was as high as 101 F. on two occasions but usually was subnormal. The pulse rate was always above 80 and ranged between 90 and 115 for several days. On one occasion it reached 140 per minute.

Treatment.—This was the same as in Case 1. The same amount of antitoxin was administered, food and laxatives were given by stomach tube and fluid was given by the Murphy drip method. A digitalis preparation was given as indicated.

Results.—Recovery in this case was very slow. On March 10, six weeks after the poisoning, the patient was still confined to bed and still was forced to take his food through a stomach tube. He had become greatly emaciated and was very weak, but muscular coordination was improved and there was no ptosis or diplopia. The skeletal reflexes were normal. There had been infection at the site of inoculation of serum and small pockets of pus were still present, although bacteriologic examination failed to show any pyogenic bacteria.

CASE 3.—*History.*—B. M., aged 13 months, ate very little of the fruit and did not show any symptoms of poisoning until Wednesday evening. At that time it was noted that there was bilateral blepharoptosis, mydriasis with little reaction to light, and apparent photophobia. There had not been any acute gastro-intestinal disturbance and the child did not appear to be in pain. The temperature was normal and the pulse rate 120.

Examination.—When seen by me on Friday, about two hours before he died, the child was apparently conscious but very apathetic. There was marked ptosis, the pupils were widely dilated and did not react to light and the skin was very dry. The heart sounds were normal and no dulness or râles were detected in the lungs. The skeletal reflexes were normal but the muscles were

all relaxed. The temperature was 99.2 F. (rectal) and the pulse rate 160. Death occurred from respiratory failure.

Necropsy Report.—Necropsy was done by me about four hours after death, and before the body had been embalmed. There was marked engorgement of the vessels of the pia mater and there were a few small hemorrhages on the surface of the pons, in the space between the cerebrum and cerebellum. There was no increase in the amount of fluid in the ventricles and the cerebral convolutions were not flattened. There was no general engorgement of the abdominal and thoracic viscera but there was beginning bronchopneumonia in the bases of both lungs. The spleen was not enlarged or soft.

Microscopic examination of the tissues showed no degeneration of the ganglion cells of the brain and cord and no thrombi in the blood vessels of the central nervous system. There were well marked patches of bronchopneumonia and many masses of cellular thrombus in the larger blood vessels of the lungs. Many of the smaller vessels contained hyaline masses in which were clumps of leukocytes.

Poisoning of the Domestic Fowls.—On Wednesday, April 29, the portion of the apricots which remained in the jar was thrown to the chickens. On Thursday several chickens showed symptoms of limber-neck and some of them died, and by Friday afternoon over twenty-five chickens and one turkey had died. A wild canary with similar symptoms was found lying under a tree and it died a few hours later.

Identification of B. Botulinus.—Bacteriologic examination of the contents of the gizzard of one of the chickens revealed the presence of a strain of *B. botulinus* which produces a virulent toxin when grown in suitable culture mediums. This strain, which we have labeled Strain 9, was shown to produce a toxin which is homologous with Toxins 3, 4, and 7 of my series.

Methods Employed in Canning.—We were unable to learn the method by which the apricots had been canned, but it is known that the fruit was unsalable, wind-fall fruit, and that Mrs. M. had marked the jars for early use as she feared the fruit would spoil. It was noted by some of those who ate the apricots that there was a peculiar sharp taste, but no unusual odor was detected.

Outbreak 12 (one case).—On Friday, Feb. 22, 1918, Mrs. H. of Oakdale, Calif., tasted a small portion of a bean pod from a jar of home-canned string beans which she had just opened. The beans had a peculiar irritating taste but she swallowed a small amount. When she placed the beans on the stove to cook there was an extremely disagreeable odor and she discarded them.

On Saturday morning, February 23, Mrs. H. was dizzy when she first got out of bed and she staggered when she walked. She noted that vision in the left eye was blurred. By afternoon vision was blurred in both eyes and the staggering was much worse. The patient became alarmed and consulted Dr. J. B. Thompson of Oakdale, to whom I am indebted for the following report.

When first seen by Dr. Thompson, Mrs. H. was almost hysterical but had no complaint other than that which has been detailed. She said that there had been no pain and no gastro-intestinal disturbance, and that she had not even been nauseated.

Examination showed complete dilatation of both pupils, which reacted very sluggishly to light, and a pulse rate of about 100 per minute. The temperature was normal. The patient was very weak and muscular movements were not coordinated, but nothing else abnormal was found. Dr. Thompson stated that he was strongly suspicious of belladonna poisoning, as at that time the patient denied having eaten any spoiled food.

After midnight, Saturday, Mrs. H. complained that her tongue was swollen, and she began to have difficulty in talking. On Sunday morning there was bilateral ptosis and later in the forenoon she began to have difficulty in swallowing. Speech rapidly became unintelligible. About noon on Sunday she

began to vomit and the vomiting continued for the greater part of the afternoon. There were three formed stools during Sunday forenoon and several involuntary liquid stools during the afternoon. All the stools were extremely offensive. There were no bowel movements during the last thirty-six hours of life. Toward evening on Sunday the patient began to have spells of strangling when she attempted to swallow, and she complained bitterly of the accumulation of mucus in the pharynx, which she was unable to raise. Urination was not disturbed except that the patient voided involuntarily during strangling spells.

The temperature varied from normal to 102.6 (rectal) just before death, respiration remained about 24 and the pulse varied from 98 to 120 per minute.

The patient was very restless and did not sleep during Sunday night or Monday. There was no disturbance of mentality and the skeletal reflexes were intact. There was no disturbance of sensation except a sense of numbness in the hands. She became rapidly weaker and the pulse increased in rapidity. At first there was satisfactory response to stimulation but later there was no appreciable effect. The patient died early Tuesday morning, about eighty-eight hours after tasting the beans.

To remove the mucus from the pharynx, Dr. Thompson made use of an aspiration bottle to which a soft rubber catheter was attached. He stated that this appeared to give much greater relief and to cause much less irritation than swabbing.

The beans which caused the poisoning were grown in Oakdale and were picked but a few hours before they were canned. They were washed, strung, broken into small pieces and boiled in an open kettle for twenty minutes. They were then packed into new, freshly-boiled, 1-pint economy jars, 1 tablespoonful of salt was added to each jar and the jars were covered, immersed into boiling water, which covered them, and boiled actively for three hours. Twelve jars of beans were canned and two of them spoiled. The contents of nine of the others were eaten after they had been cooked, and appeared to be good, but there is no record as to whether any one had eaten or tasted any of the beans before they were cooked. One jar was taken to the laboratory for bacteriologic examination, but no evidence of *B. botulinus* was found.

A portion of the beans from the contaminated jar was gathered from the garden where they had been thrown and had lain in the rain for several days. Bacteriologic examination showed no evidence of *B. botulinus*.

Outbreak 13 (one case).—On Sunday, Feb. 17, 1918, Mrs. K. of Los Angeles, opened a jar of string beans which she had canned during the past summer. She tasted four of the beans and noted that they had a peculiar taste which she at first attributed to the presence of some lemon juice which had been added to the beans when they were canned. She eventually decided that they were not good, and discarded them.

On Monday morning Mrs. K. "was distressed" and took a small dose of Epsom salts. Toward evening she vomited, and then took a large dose of Epsom salts, after which the bowels moved several times. On Tuesday she was worse, and consulted Dr. Thomas C. Myers of Los Angeles who sent me the record of the case.

When Dr. Myers first saw Mrs. K. she was extremely nervous and complained of double vision and of "swelling in the throat," dryness of the mouth and difficulty in talking and swallowing. There was marked muscular weakness and bilateral ptosis but the pupils were not dilated. The temperature was subnormal and the pulse was rapid. The patient died early Wednesday morning, about sixty hours after she had tasted the beans.

A portion of the discarded beans was recovered from the garbage can, several days after they had been discarded, but bacteriologic examination failed to show the presence of *B. botulinus*.

The beans were canned by Mrs. K. during the past summer. The exact method of canning could not be obtained, but it was known that the beans were washed, broken and packed into 1-quart, self-sealing Mason jars, and

that 1 teaspoonful of salt and "a small amount" of lemon juice were added to each jar. The jars were filled with cold water and the covers placed in position, after which they were placed in a wash-boiler and "steamed for three hours." It was impossible to find out whether the jars had been immersed in boiling water or whether they were merely steamed, nor could we learn whether the three hours was estimated from the time the jars were placed in the wash-boiler or from the time the water commenced to boil.

Outbreak 14 (one case).—On Sunday, March 10, 1918, Mr. A. Y. of Colton, Calif., ate home-canned pears which had a peculiar taste. On Monday afternoon he complained of a sensation of swelling of the tongue, and of vomiting. In the evening he consulted Dr. J. S. Champion of Colton, who sent me the record of the case.

Mr. Y. complained of indistinctness of vision, diplopia and vertigo and stated that he was unable to walk straight. There was some difficulty in swallowing and in talking, articulation being so indistinct that it was difficult to understand what was said. There was ptosis of the left eyelid.

There was moderately severe constipation although the bowels moved freely after the administration of Epsom salt. Diplopia and vertigo persisted for over three weeks, but after a few days the patient was able to swallow liquids, although it was impossible to swallow solids. At first there was some annoyance from an accumulation of thick mucus in the pharynx but this did not persist. The temperature ranged between 97.6 and 99.6 F., and the pulse between 60 and 112. It is interesting that the pulse rate gradually increased from 60, the rate when the patient was first seen, to 112 on the third day.

Mentality was clear throughout, but this case is of interest in that there was a persistent numbness of the left side of the body. At the end of three weeks the patient was much improved, although there were still some eye symptoms and marked weakness.

It was not possible to determine beyond a possibility of doubt that the pears were the cause of the poisoning since it is not known whether other persons partook of the same pears without suffering ill effects. Neither was it possible to learn the method which was adopted in canning the pears, but there was no record of the patient having eaten any other food which gave any indication of being spoiled.

B. Report of Instances in Which Domestic Fowl and Animals Were Poisoned by Feeding Spoiled, Home-Canned Vegetables

In our investigation of outbreaks of food poisoning caused by home-canned products we have obtained records of at least ten outbreaks of poisoning of domestic animals and fowl caused by feeding spoiled, home-canned vegetables. These are in addition to ten other instances in which the poisoning of the animals and fowl occurred coincidently with outbreaks of poisoning of human beings, the animals and fowl having been poisoned by feeding them remnants of the food which had caused the poisoning of the human victims, and to several other instances in which it was believed that the poisoning was due to feeding spoiled home-canned products, although we were unable to obtain sufficiently accurate details to justify making a definite conclusion that such was the case. Six of these ten outbreaks were caused by feeding spoiled home-canned string beans, three by feeding spoiled home-canned corn and one by feeding spoiled home-canned green peas.

CAUSE OF THE POISONING CONFIRMED

The reasons for assuming that these outbreaks of poisoning of domestic animals and fowl were dependent on the presence of the toxin of *B. botulinus* in the spoiled home-canned products are the following: (1) The symptoms were identical with those which occurred in animals and fowl which had been poisoned by food which had caused typical botulinus intoxication of human beings, and in which *B. botulinus* was recovered from remnants of the discarded food; (2) it has been shown that symptoms identical with those which were observed in these animals and fowl may be produced experimentally by feeding the toxin of *B. botulinus* to domestic animals and fowl,[3] and (3) in one instance recorded in the following (Outbreak 1) we were able to demonstrate the presence of botulinus toxin in remnants of the mash which was fed to the chickens and to recover *B. botulinus* from the crops and gizzards of two of the chickens which died as well as from three out of six jars of the same lot of string beans which remained in the vegetable closet.

Four instances of poisoning of domestic animals and fowl are detailed because of the fact that the methods by which the vegetables were canned have been ascertained.

CASES OF POISONING IN DOMESTIC ANIMALS

OUTBREAK 1.—On Feb. 12, 1918, Mrs. M. of Berkeley, Calif., opened a jar of home-canned string beans and noted that they had an unpleasant odor, "something like cheese." She mixed the beans with a mash which she was preparing and fed them to the chickens. Eleven of her twelve chickens developed typical symptoms of limber-neck and died.

Six jars of beans which remained in the vegetable closet and the carcasses of several of the chickens as well as a portion of the mash which remained over, were taken to the laboratory for examination. From the crops and gizzards of two of the chickens and from three of the jars of beans a virulent strain of *B. botulinus* was recovered, and in the mash it was found that there was still a virulent toxin present. The toxicity of the beans in the jars was comparatively high, 0.001 c.c. of the filtered bean juice being sufficient to kill a 250 gm. guinea-pig within twenty-four hours. This toxin was shown to be homologous with that of Strain 6 of my series, thereby differing from all other strains which have been isolated on the Pacific Coast.

The beans were grown by Mrs. M. in her own garden and were picked but a few hours before they were canned. They were washed, broken into small pieces and packed into 1-quart Mason jars. The beans were covered with cold water and were sterilized by leaving the jars immersed in boiling water in a wash-boiler for two and one-half hours on each of three consecutive days. Mrs. M. does not remember whether the jars were sealed during the intervals

3. Dickson, E. C.: Botulism: A Cause of Limber-Neck in Chickens, Jour. Am. Vet. Med. Assn., 1917, **50** (New Series III), 612. Buckley and Shippen: Preliminary Report on the Relation of Anaerobic Organisms to Forage Poison- Am. Vet. Med. Assn., 1917, **50** (New Series III), 612. Buckley and Shippen: Preliminary Report on the Relation of Anaerobic Organisms to Forage Poisoning, ibid., 1917, **50** (New Series III), 809. Graham, Bruekner and Pontius: Studies in Forage Poisoning V and VI, Kentucky Agricult. Exper. Sta., Bull. 207, 1917.

between sterilizations, as she had been told that it made no difference whether they were sealed or left open.

Outbreak 2.—On Feb. 15, 1918, Mrs. L., near Hollister, Calif., noticed that one of her hogs was dragging its hind legs and that it could not eat. On the following day the hog was down and could not get up. When disturbed it tried to squeal but was unable to do so. It remained in the same position for several days and it was noted that there had been no evacuation of the bowels during that time.

About three days later another hog became affected in the same way and Mrs. L. called in Dr. C. S. Brooks of Hollister, the county veterinarian. It was through the courtesy of Dr. Brooks that I was permitted to see these animals.

The symptoms of both hogs were the same; they first dragged their hind legs, eventually went down and could not rise, were unable to eat although they tried to do so, were unable to squeal and were constipated. The pupils were dilated and did not react to light, the temperature was normal and heart beat rapid. Both animals were given Epsom salt with good results. Both remained in the same condition for about one week and then gradually recovered. Within two weeks they were able to move around, to squeal and to eat.

It was learned that the hogs had been fed the contents of a jar of home-canned green peas which had spoiled and which had a very offensive odor. None of the peas were fed to chickens or to other animals.

The peas had been grown by Mrs. L. and had been placed in 1-quart Mason jars and sterilized by immersing the jars into boiling water in a wash-boiler for three hours. All Mrs. L.'s vegetables had been canned by the same method and there had been a considerable amount of spoilage.

There may be some doubt as to whether the illness of the hogs was really due to poisoning with botulinus toxin as hogs are supposed to be immune to botulinus intoxication. However, the symptoms were identical with those which we have produced experimentally by subcutaneous injections of the toxins of our Strains 3 and 4 of *B. botulinus*, and a virulent strain of *B. botulinus* was recovered from a jar of spoiled string beans which was canned in the same way and which remained in Mrs. L.'s cellar.

Outbreak 3.—During the summer of 1917, Mr. H. of San Jacinto, Calif., canned several jars of corn by the fractional method of sterilization, in which he closely followed the instructions given in U. S. Department of Agriculture Farmers' Bulletin No. 359. About one month later he noticed that some of the corn was spoiling and that there was gas formation. He discarded the whole lot and fed it to the chickens. Within from twelve to twenty-four hours a number of his chickens developed typical symptoms of limber-neck, and within two or three days fifty-eight out of sixty-six died. Mr. H. stated that he had no way of knowing whether the eight survivors had eaten any of the corn.

It was not possible to obtain material for bacteriologic examination.

Outbreak 4.—In January, 1918, Mrs. L. of Raymond, Calif., threw out five jars of home-canned food which had spoiled, three 1-quart jars of peas, one 1-quart jar of string beans and one 1-pint jar of beef. The contents of all the jars had an offensive odor and were not eaten or tasted by human beings.

Within a few hours after eating the discarded food, eighty-one chickens developed typical symptoms of limber-neck and seventy-two of them died in from one to three days. Mrs. L. stated that the survivors had each been given a tablespoonful of castor oil.

The food was canned by Mrs. L. who stated that very little of her canned goods had spoiled. The material was packed in 1-quart Mason jars which had been boiled, and was cooked and sterilized by immersing the jars into boiling water in a wash-boiler for three hours.*

* This outbreak is not included in the series of ten recorded as being due to home-canned vegetables, as there is a possibility that the meat was at fault.

COMMENT

A study of these cases as well as of those described in my previous report[1] fully justifies the conclusion that the use of home-canned food is not wholly unattended with danger. In the instances which have been cited, various methods of canning were adopted and were followed as carefully as it is possible to have untrained persons conduct technical procedures. The fact that in several instances the greater part of the home-canned material remained in good condition simply proves that though the methods are efficient in preventing ordinary spoilage, they are inefficient if the raw material happens to be contaminated with spores of *B. botulinus*. It has been stated that it is essential that only freshly picked raw material should be used for canning and that it should be blanched before it is placed in the jars, but Outbreak 12 shows clearly that three hours' sterilization in the washboiler is not sufficient to kill spores of *B. botulinus* in vegetables which had been freshly picked and had been boiled for twenty minutes in an open kettle before being packed into 1-pint jars, a procedure which should be at least as efficient as simple blanching.

These cases also illustrate the fact that it is unsafe to eat or even taste home-canned products before they have been boiled. In six outbreaks of botulism the victims were poisoned by simply tasting home-canned goods to determine whether they had spoiled, and in several others the poisoning was caused by the ingestion of salads prepared from uncooked, home-canned vegetables. It is well known that the toxin of *B. botulinus* is quickly destroyed by heat and Outbreak 8 is an illustration of this fact, since those who ate the cooked asparagus on Sunday night remained in perfect health, whereas the man who ate the remainder of the asparagus from the jar, uncooked, on Monday night, developed the typical symptoms of botulinus intoxication.

It is not the object of this report to discourage the home-canning of fruits and vegetables or to interfere in any way with the active campaign for the conservation of perishable foods. It is of the utmost importance, however, that those who are directing the home-canning industry should recognize that the present methods of home-canning are not entirely safe, especially in the hands of untrained workers. If they will but admit this fact and will instruct the public that there is possible danger of poisoning from home-canned products, and that the danger may be averted if all home-canned food is boiled before it is eaten or even tasted, outbreaks of botulism from home-canned products will entirely cease.

Sacramento and Webster Streets.

THE NATURE AND INTERPRETATION OF THE COLLOIDAL GOLD REACTION *

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Owing to the complexity of structure and function of the central nervous system its disorders manifest themselves in clinical pictures of the utmost variety. Furthermore, in the case of one large group of these affections, the syphilitic and parasyphilitic diseases, it is highly desirable to recognize their nature as early as possible in order that the necessary treatment may be begun and the progress of the malady be arrested before destructive lesions have supervened. The difficulties of diagnosis are consequently often very great and all suitable methods of investigation yielding objective results are therefore likely to be of much assistance, particularly if they aid not only in diagnosis, but also in observing the effects of treatment. Among such procedures are the various methods of examining the cerebrospinal fluid, such as determining the pressure under which it is held in the spinal canal, counting its cells, testing its globulin content, and carrying out the Wassermann reaction. To this list the experience of the last few years has added another, the colloidal gold reaction, and the observations so far reported indicate that it has a definite value in supplementing the information to be derived from the older sources. It is the intention here to present the results obtained in examining over two hundred cases from a general hospital service in which the colloidal gold reaction of the spinal fluid was tested over 400 times, and to compare these results with those of the other tests.

In order to understand the mode of action of the test it is necessary to step aside for a moment into the domain of the physical chemist, for the colloidal gold reaction is quite different in its principle from the ordinary test tube experiment and involves physical laws not usually called into action in the clinical laboratory.

When Thomas Graham,[1] in 1861, published his observations on colloids and crystalloids, he apparently regarded them as belonging to wholly different classes, for he said that "They appear like different worlds of matter," two fundamental distinctions being that colloids

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* From the Department of Medicine, Columbia University, and St. Luke's Hospital.

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1. Phil. Tr., Roy. Soc., London, 1861, **151,** 183.

do not crystallize, and are unable to pass through the parchment paper septum of a dialysing apparatus. Recent observations indicate, however, that the distinction is one of condition rather than of kind, for under appropriate circumstances many, if not most, substances, can be made to assume either form[2] and it is therefore preferable to speak simply of the colloidal state, rather than of colloids as a class. In a colloidal solution or heterogeneous system, as it is called, in distinction to the solution of a crystalloid, or homogeneous system two components or phases are recognized, the internal or dispersed phase, and the external or continuous phase. Such systems may be composed of solids, liquids, or gases in various combinations. For example, in fog a liquid is the internal phase and a gas the external phase, while in the foam on a glass of beer, the conditions are reversed. In the smoke of a cigaret a solid is dispersed in a gas, in currant jelly a liquid is dispersed in a solid, in a piece of ruby glass copper is dispersed in another solid, and finally, in the gold reagent under discussion a solid forms the internal phase and a liquid the external phase.

Evidently it is not only jellies or substances of a gluey or colloidal nature in Graham's sense that can assume the colloidal state. Solids also, that ordinarily are regarded as entirely insoluble, may be brought into a state of such minute subdivision that their particles remain suspended indefinitely in a fluid medium without settling out, and are then termed suspensoids. They have reached ultramicroscopic dimensions, and approach the molecule in size; that is, they are less in diameter than the wave lengths of the visible spectrum which lie between 700 and 400 microns. An object smaller than half the wave length of the light by which it is illuminated cannot be seen in its true form, for the light is not reflected from its surface, any more than a wave can be reflected from a pebble on the beach, and consequently a colloidal solution appears homogeneous on inspection and the particles of the suspensoid remain invisible, even with the highest magnification. When viewed with the ultramicroscope, however, in which intense lateral illumination is employed, the true nature of the system is revealed, for under these conditions even ultramicroscopic particles become visible by virtue of the Tyndall phenomenon, just as otherwise inappreciable motes may be seen dancing in a ray of sunlight entering a darkened room.

One of the ways in which colloidal solutions or heterogeneous systems differ from ordinary solutions or homogeneous systems is in the fact that in the former there are faces of contact between the external and the internal phase. Consequently the forces of surface tension

2. Bayliss: Principles of General Physiology. London, Longmans, Green & Co., 1915, p. 109.

are brought into play, and affect the behavior of the solution. This is especially so since the area of the suspensoid has been increased to an almost unbelievable extent by its transfer to the colloidal state. A sphere of gold 2 mm. in diameter has a surface of 0.126 square cm., while the surface of the same mass if reduced to colloidal particles having a diameter of 10 micromicrons would have an area of about 100 square meters, or ten million times as much.[3] Siedentopf and Zsigmondy have obtained gold dispersoids with particles of a diameter of less than 6 micromicrons (that is, 6 millionths of a millimeter). For comparison it may be stated that the molecules of starch are estimated to have a diameter of about 5 micromicrons, those of chloroform and of sugar about 0.8 micromicrons, those of carbon dioxid and of sodium chlorid about 0.3, while the molecule of hydrogen gas, which appears to be the smallest of all, measures only about 0.1 micromicrons.[4] Gravity has no effect on these suspended particles, which are prevented from settling out of the fluid by the action of forces akin to those responsible for the Brownian movement observed when particles large enough to be visible under high magnifications are examined in a fluid medium under the microscope. Perrin[5] has shown that this is essentially the same as the molecular movement of the medium in which the particles are held and that it is due to the continual molecular bombardment to which they are subjected. In addition, the electrical charges of the colloidal particles are of importance, particularly in connection with their behavior when brought into contact with solutions of electrolytes. If to a colloidal system holding a suspensoid in this state of equilibrium a solution of a neutral salt, that is, containing ions in the dissociated state, is added, the colloidal particles unite to form groups or aggregates and are precipitated. This may be explained on the supposition that the ions having the opposite electric charge to the colloidal particles become concentrated on the surface of the particles and impart their charge to these, rendering them sensitive to the presence of ions of opposite charge. These in turn neutralize the charge on the particle, and cause the formation of aggregates with resultant precipitation, the effect being the greater the higher the valence, that is, the number of electrical charges, of the ion in question. Occurring on a gigantic scale, this process of flocking out of suspensoids by the action of electrolytes is responsible for the production of the Mississippi river delta through the precipitation of the colloidally suspended particles in the turbid river water which takes place as it mixes with the highly saline waters of the Gulf, while in miniature the chemist utilizes the

3. Bayliss: Principles of General Physiology, 1915, p. 89.

4. Ostwald: A Handbook of Colloid Chemistry. Philadelphia, P. Blakistons Son and Co., 1915, p. 31.

5. Perrin: Comptes rend. de l'Acad. Française, 1908, **146**, 967.

same physical forces when he obtains a water-clear filtrate from a test tube full of blood to which he has added dialyzed iron and a solution of magnesium sulphate.

But still another peculiarity of colloidal solutions has to be considered before we are ready to comprehend the behavior of the reagents in the gold test. If a trace of an emulsoid or reversible colloid like gelatin is added to a solution containing a suspensoid the precipitating action of salt solutions is nullified, and the suspensoid solution is said to be in the protected state. It appears that this protective action is due to the deposition of a film of the emulsoid over each particle of the suspensoid, thus practically converting it into an emulsoid system which is no longer susceptible to flocculation by electrolytes. This principle has been made use of by Schulz and Zsigmondy[6] in establishing a so-called gold number for the different proteins. This is the number of milligrams of the given protein required to protect 5 c.c. of colloidal gold from flocculation by 0.5 c.c. of 10 per cent. sodium chlorid solution. It has been found to be a very delicate reaction, and may be used for the quantitative determination of albumins in solution, or for their identification if in pure form. The results of the gold reaction on the spinal fluid appear to depend to some extent at least on differences in the respective protective and precipitating powers of the albumin and globulin of the spinal fluid, the former acting as a protective agent and the latter as a precipitant.

After this brief excursion into the field of physical chemistry we are in a better position to understand the application of the gold reaction to the spinal fluid. The main reagent used is the gold solution, having a beautiful ruby color already familiar to everyone in the splendid hues of cathedral windows, whose wonderful glowing reds are due to colloidal gold in the glass. Faraday, in 1858, made such solutions by the reduction of gold chlorid with phosphorus and carbon disulphid, and a specimen prepared by him is still on view in the Royal Institute in London. Zsigmondy, the same investigator who developed the ultramicroscope while studying the chemistry of glass manufacture, found that better results could be obtained by using formaldehyd as the reducing agent, together with potassium carbonate,[7] and various modifications of this method have been suggested. Through a lack of understanding of all the factors concerned, much difficulty has been experienced in obtaining proper solutions, for unless the reagent conforms to certain definite requirements it is valueless, and to secure these has been found so difficult that one author

6. Schulz and Zsigmondy: Beitr. z. Chem. Phys., 1903, **3,** 137.
7. Zsigmondy: Liebig's Ann. d. Chem., 1898, **301,** 29; Ztschr. f. analyt. chem., 1901, **40,** 697.

(Glaser[8]) has gone so far as to say that owing to the uncertainty of being able to prepare a satisfactory reagent the method is unsuited for practical use, and others have described rather complicated methods of manufacture.[9]

TECHNIC

Colloidal solutions of gold may be obtained in various ways, by reduction, oxidation, hydrolysis, condensation, or dispersion, the latter being effected either by chemical or by electrical means. The method that has been found most practical for the present purpose is that of reduction of gold chlorid in alkaline solution by the action of formaldehyd and oxalic acid. The reagents required are a 1 per cent. solution of gold chlorid, a 2 per cent. solution of potassium carbonate, a 1 per cent. solution of oxalic acid, and a 2.5 per cent solution of formaldehyd. To make a liter of the solution, 10 c.c. of the 1 per cent. gold chlorid solution, 7 c.c. of the 2 per cent. potassium carbonate solution, 1.75 c.c. of the 1 per cent. oxalic acid solution, and 0.83 c.c. of the 2.5 per cent. formaldehyd are added to a liter of distilled water in a chemically clean flask. After thorough mixing the fluid is heated to from 80 to 85 C. and kept at that temperature until a series of color changes has taken place, running through gradations from faint blue-green to a deep ruby-red. When the solution reaches its maximum depth of color a remarkable lightening in hue occurs within the space of a few seconds, the dark ruby red becoming converted to a lighter shade, and when this stage is reached, the fluid in thin layers has an orange pink color, and the reaction is finished. If the solution is properly made, 5 c.c. will be completely precipitated in one hour by 1.7 c.c. of a 1 per cent. sodium chlorid solution, showing that it is not "protected," that is, kept from precipitation by electrolytes through the protective action of impurities. In addition, it must give characteristic results with known normal, paretic, and luetic spinal fluids. Full details in regard to a rapid and simple method for preparing the solution may be found in the St. Luke's Hospital Guide to Laboratory Technique[10] and in an article from this laboratory by O. I. Lee.[11]

To carry out the test, into the first of a series of eleven heavy glass, lipless test-tubes (measuring about $11/16$ by 6 inches) 1.8 c.c. of 0.4 per cent. sodium chlorid solution is measured and into each of the remaining ten, 1 c.c. Of the spinal fluid to be tested, 0.2 c.c. is then introduced into the first tube; 1 c.c. of the mixture is placed in the second tube; 1 c.c. of this mixture in the third, and so on up to and including the tenth tube, from which, however, the 1 c.c. withdrawn is rejected, leaving the eleventh tube as a color control. The concentration of the spinal fluid thus ranges from 1:10 in the first tube to 1:5,120 in the tenth. To each of the eleven tubes is then added 5 c.c. of the colloidal gold solution and the tubes are shaken with a rotary motion to secure thorough mixing.

At the end of half an hour the color of each of the ten tubes is matched against a diffuse white background with the nearest shade selected from the color scale, using the eleventh tube for comparison.

The red or unaltered fluid is given a value of 0, red-blue 1, violet-blue 2, blue 3, pale-blue 4, colorless 5. These color values are then plotted as the

8. Glaser: Neurol. Centralbl., 1914, **32,** 688.

9. Miller, Brush, Hammers and Felton: Bull. Johns Hopkins Hosp, 1915, **26,** 391.

10. Wood, F. C., Vogel, Karl M., and Famulener, L. W.: Laboratory Technique. The Methods Employed at St. Luke's Hospital. Ed. 2. New York: James T. Dougherty, 1917, p. 86.

11. Lee, O. I.: A Simple Procedure for the Preparation of Colloidal Gold for Diagnostic Purposes, Am. Jour. Med. Sc., 1918, **155,** 404.

abscissae against the dilutions as ordinates, so as to make a continuous curve, and this constitutes the preliminary reading. At the end of twenty-four hours the values are again read, and this is designated as the final curve, which is usually parallel to the preliminary curve, though a little higher in the scale.

Different affections of the cerebrospinal system produce changes in the spinal fluid which bring about flocking out of the gold solution in different concentrations of the spinal fluid, the varying degrees of precipitation of the gold being characterized by changes in the color of the supernatant fluid, owing to variations in the size of the aggregates of gold resulting, the color becoming bluer as the size of the particles increases. These changes have been found to be fairly consistent, so that it has been possible to establish definite curves or zones of precipitation which seem to be sufficiently reliable to permit of definite diagnostic conclusions, particularly in the case of paresis, tabes, cerebrospinal syphilis and meningitis.

We have records of over 200 cases in which the reaction was performed more than 400 times. This series is of particular interest, because in addition to the syphilitic and parasyphilitic conditions, it comprises so many others of a miscellaneous nature.

Tabes.—The gold reaction is of particular interest in tabes, and of our twenty-four cases, all gave distinctly pathologic curves. The

TABLE 1.—TABES DORSALIS—TWENTY-FOUR CASES

Case No	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
177	11/ 9/16	++++	+?	0	3	1 1 1.52 3 3 1.51 0 0	Specific aortitis
	11/19/16	++++	+	0	4	1 1 2 2 3 3 2 2 0 0	Arteriosclerosis
	1/ 2/17	++++	+	±	4	0 1 1 0 1 1.51 2 1 1	
	3/27/17	++++	0	+	8	1 1 2 2 3 2 1 0 0 0	
	5/22/17	++++	++	+	180	4 4 3.53 2 1.50 0 0 0	
178	11/ 9/16	+	++++	0	4	1 1 2 3 3 1.51 0 0 0	
	11/19/16	+++	++++	0	10	1 1 2 2 3 3 2 0 0 0	
	12/11/16	+++	+++	++	2	1 1 1 2 3 3 2 1 0 0	
	12/27/16	....	....	++	216	0 0 0 1 1.52 1.51 0 0	
	1/31/17	+++	++	0	2	1 1 2 3 2 0 0 0 0 0	
	2/ 2/17	+++	++++	0	3	1 1 1 2 2 2 1 0 0 0	
	3/ 8/17	+	++	+	6	1 1 1 2 2 0 0 0 0 0	
	4/ 6/17	+	++	0	4	1 1 2 3 2 1 0 0 0 0	
	5/22/17	+	++	0	3	2 2 3 3 1 1 0 0 0 0	
	6/13/17	±	++	+	....	1 1 1 2 1 0 0 0 0 0	
	8/14/17	+	±	±	8	1 1 2 2 0 0 0 0 0 0	
	10/31/17	+	++	+	9	0.50.51 1 0.50.50 0 0 0	
179	4/20/17	A.C.	+	+	9	1 2 3 2 1 1 1 1 0 0	

TABLE 1.—TABES DORSALIS—TWENTY-FOUR CASES—(*Continued*)

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test										Remarks
		Blood	Spinal Fluid													
180	1/31/17	0	0	+	....	1	1	1	1	1	1	3	3	2	1	Previous treatment
	2/ 3/17	0	....	....	....	1	1	1	1	1	1	0	0	0	0	
	2/11/17	0	0	+	20	3	2	1	2	3	0	1	0	0	0	
181	9/19/16	+	++++	+	35	5	4	0	1	2	3	1	1	1	0	Tertiary syphilis; pyelitis; pyelonephrosis; general septicemia at death
	11/11/16	+	....	+	12	1	1	1	1.5	2	3	2	1.5	1.5	1	
	5/ 8/17	+++	++++	Faint+	10	1	1	1	3	2	0	1	1	0	2	
182	7/12/17	0	+++	0	4	5	2	2	4	3	2	1	0	0	0	
	7/17/17	....	....	....	10	4	4	4	4	4	2	1.5	1	1	0	
	9/14/17	+	0	?	10	2.5	3	4	3	2	1	0	0	0	0	
	11/ 9/17	0	++	0	3	5	4	3	2.5	2	0.5	0	0	0	0	
183	11/ 4/16	0	0	0	3	1	1.5	1.5	2	1.5	0	0	0	0	0	
184	5/19/17	....	0	+	26	1	2	3	4	3	2	1	0	0	0	Charcot joints
185	1/29/17	+++	++++	0	11	2	2	2	3	2	2	0	0	0	0	Tertiary syphilis; chronic bronchitis
	2/ 3/17	....	A.C.	0	24	1	1	2	2	3	3	2	1	0	0	
	3/ 7/17	++++	++++	0	8	1	1	2	2	3	2	1	0	0	0	
186	1/ 7/17	A.C.	++	+	4	1	1	2	3	3	2	1	0	0	0	
	4/13/17	0	....	0	15	1	2	4	3	3	1	0	0	0	0	
187	10/10/16	0	0	±	6	1	1	1	1	1	0	0	0	0	0	Cerebrospinal syphilis. Previous treatment
	10/16/16	0	0	+	6	1	1	1	1	1.5	1.5	0	0	0	0	
	11/24/16	0	0	0	4	1	2	2	2	1	0	0	0	0	0	
	1/ 9/17	0	0	0	4	1	1	1	2	1	1	0	0	0	0	
	3/17/17	0	0	0	3	1	1	2	3	1	0	0	0	0	0	
	4/24/17	±	0	0	4	1	1	2	2	2	1	0	0	0	0	
	6/ 5/17	0	0	0	4	2	2	3	3	3	1	1	0	0	0	
	7/ 5/17	0	0	0	4	1	1	2	1	0	0	0	0	0	0	
	8/17/17	0	0	0	4	1	1	1	1	0	0	0	0	0	0	
	10/13/17	0	0	+	15	1	1	1.5	1.5	1.5	0	0	0	0	0	
	11/13/17	0	0	....	....	1	1	0.5	0.5	0.5	0	0	0	0	0	
188	7/20/16	+++	++	+	24	0	1	2	1.5	2	1	0	0	0	0	Previous treatment
	9/19/16	+++	0	0	1	0	0	0	0	1	1	0	0	0	0	
	10/10/16	+	±	0	30	1	1	1	1	1	1	1	0	0	0	
	10/31/16	+	....	0	3	1	1	1	1.5	1.5	0	0	0	0	0	
	11/21/16	+	0	Faint+	7	1	1	1	1	2	2	2	0	0	0	
	12/12/16	+++	0	Faint+	8	1	1	1	1	2	2	0	0	0	0	
	1/ 3/17	+	0	0	3	1	1	2	2	2	2	3	1	0	0	
	1/26/17	+	0	0	6	1	1	1	1	1	0	0	0	0	0	
	4/16/17	+	±	0	0	1	1	2	2	0	0	0	0	0	0	
	5/ 7/17	+	0	0	10	1	1	1	1	1	0	0	0	0	0	
	5/29/17	±	0	0	4	1	1	1	1	1	0	0	0	0	0	

TABLE 1.—TABES DORSALIS—TWENTY-FOUR CASES—(*Continued*)

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
189	5/24/17	0	0	....	1	2 3 4 3 3 2 1 0 0 0	Thrombosis of veins in right arm; cellulitis
	6/22/17	....	0	+	2	1 1 2 2 3 1 1 1 0 0	
190	9/18/16	+++	+++	0	11	5 5 1.5 4 1.5 1.5 1 0 0 0	Previous treatment
191	2/ 2/17	0	++++	0	6	2 2 2 2 3 3 2 1 0 0	Previous treatment
	2/17/17	0	++	+	4	5 2 3 4 4 3 1 0 0 0	
	3/ 9/17	0	....	+	....	1 1 2 3 4 3 1 0 0 0	
	4/11/17	±	++++	+	8	1 1 2 3 4 3 1 0 0 0	
	4/25/17	0	++	0	10	1 1 2 3 3 3 2 1 0 0	
	5/ 6/17	0	++	Faint+	12	1 1 1 2 3 2 1 1 0 0	
	6/11/17	±	++	0	10	1 1 2 1 3 1 1 0 0 0	
192	4/ 5/17	+	++++	Faint+	50	2 2 3 4 4 3 2 1 0 0	
	5/17/17	0	+	+	7	4 3 4 5 4 3 2 1 0 0	
	8/18/17	0	0	....	....	1 1 1 2 1 0 0 0 0 0	
	10/23/17	0	0	0	4	0.5 1 2 2 0.5 0 0 0 0 0	
193	7/ 3/17	++++	0	0	4	1 1 1 0 0 0 0 0 0 0	Chronic endocarditis; mitral stenosis and insufficiency
	8/12/17	++++	0	+	20	1 1 1 2 2 0 0 0 0 0	
	8/22/17	++++	0	....	10	1 1 2 2 1 0 0 0 0 0	Cardiac dilatation and hypertrophy
	9/16/17	++++	0	0	9	1 1 1.5 2 2 1 0 0 0 0	Tertiary syphilis
194	9/27/17	0	0	±	2	1 1 1.5 2 2 1.5 0 0 0 0	Previous treatment
195	12/26/16	....	±	+	3	1 1 2 3 4 3 2 1 0 0	
	12/31/16	+	+	++	20	0 0 0 1 1 1 1.5 0 0 0	
	6/ 5/17	0	±	0	8	1 1 1.5 1.5 1.5 1 0 1.5 1.5 1.5	
	7/28/17	0	0	0	7	1 1 2 2 1 0 0 0 0 0	
196	7/24/17	0?	0	....	....	1 1 1 1 2 3 2 1 0 0	
198	10/ 7/16	0	0	0	3	0 0 0 1 1 1 0 0 0 0	
	12/21/16	+	0	±	13	1 1 3 3 3 2 1 0 0 0	
	3/ 8/17	0	0	0	5	1 1 1 1 1 1 0 0 0 0	
	4/14/17	0	0	0	10	1 1 2 3 2 1 0 0 0 0	
	6/21/17	0	0	+	5	1 1 1 2 1 0 0 0 0 0	
	8/ 9/17	0	0	0	4	1 1 2 2 1 0 0 0 0 0	
	11/ 6/17	0	±	+	8	0.5 1 2.5 3 2 1.5 1 5 0 0	
199	3/25/17	0	+++	+	98	1 2 1 1 2 4 4 1 0 0	
201	5/27/17	0	0	0	5	1 1 2 2 2 3 2 1 0 0	
202	11/ 1/17	+++	++	+++	36	1 1 2 3 2 1 0.5 0 0	

curve in most cases was in the syphilitic zone, though with a tendency to be displaced somewhat to the right, and in not quite half of the cases the peak of the curve reached 4 on the color scale. In one case (No. 180) one curve obtained was of the meningitic type, while a

later one was in the paretic zone, and two other patients (182 and 190) also gave paretic curves. In both of these, the Wassermann[12] was positive in both the blood and spinal fluid, but the globulin reaction was negative and the cells were not increased. Of the 24 cases, the blood Wassermann was negative in 8 and doubtful in 2, but 5 of these had already had active antisyphilitic treatment. The spinal fluid Wassermann was negative in 9, and doubtful in 1 case, and 3 of these were cases in which there had already been active treatment. The globulin reaction was negative in 5 cases, and the cells were below 10 in 5 cases. The gold reaction was therefore by far the most reliable index of the pathologic condition of the spinal fluid. In 9 cases in which repeated examinations were made at intervals while the patients were undergoing treatment by the intraspinal injection of arsphenamized serum, a distinct progressive flattening of the curves could be seen, which was in accord with the change in the clinical condition, and appears to be an objective indication of improvement which is rather more delicate than the decrease in the cells and in the globulin reaction.

Cerebrospinal Syphilis. — There are 22 cases of cerebrospinal syphilis in our series. The blood Wassermann was positive in 9, negative in 7, and doubtful in 4 cases, and in 2 the reaction was not determined. The spinal fluid Wassermann was positive in 15, negative in 5, and doubtful in 2 cases. The globulin reaction was positive in 19 and negative in 3 cases, and the cells were over 10 in 13, and 10 or under in 9 cases. The gold reaction was pathologic in all cases but 2, though the average elevation of the peak was not quite so high as that in tabes. In the latter condition 4 or over in the color scale was reached in 46 per cent. of the cases, and 3 or over in 83 per cent., while in cerebrospinal syphilis the respective figures are 31 per cent. and 72 per cent. The distinction, however, has not very much differential diagnostic value. In two cases the gold curve was only of the irritation type; that is, with no tube showing a color value greater than 1.5. In both of these the globulin reaction was positive; in one the blood Wassermann was positive, but the spinal fluid Wassermann was negative, while in the other, the spinal fluid Wassermann was positive and the blood Wassermann was not tested. Here again the gold reaction appears to be the most reliable single test, though the globulin reaction is little behind it in value.

12. The Wassermann reactions were performed under the direction of Dr. L. W. Famulener. The technic included the use of an antisheep hemolytic system and waterbath fixation. Two antigens were used, namely, the Noguchi acetone-insoluble, and alcoholic extract of guinea-pig heart, and in each case the reaction was performed in duplicate with two different specimens of antigen.

TABLE 2.—CEREBROSPINAL SYPHILIS—TWENTY-TWO CASES

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test										Remarks
		Blood	Spinal Fluid													
105	5/17/17	0	+	+	80	1	1	1	1	1	2	2	1	1	1	
	6/ 1/17	0	0	+	....	1	2	3	2	2	2	0	0	0	0	
	6/21/17	0	0	+	1	1	2	3	2	2	2	0	0	0	0	
	9/13/17	0	0	....	7	1	1.5	2	2	1	0	0	0	0	0	
106	8/29/17	++++	++++	0	3	1	1	1	2	3	3	2	1	1	0	
	9/ 8/17	++++	++++	+	4	1	1	1	1.5	1.5	2	1	1	0	0	
	9/16/17	....	....	....	6	1	2	2.5	3	3	2	2	0	0	0	
107	6/19/17	0	+++	+	50	2	3	3	3	2	1	1	0	0	0	
	8/10/17	0	0	+	12	1	2	3	3	2	1	0	0	0	0	
108	11/ 7/16	0	0	0	1	1	1	.5	1.5	1	0	0	0	0	0	
	12/ 3/16	....	....	Faint+	14	1	1	1	1	1	1	0	0	0	0	
	1/ 9/17	0	0	0	3	1	1	1	1	0	0	0	0	0	0	
	2/10/17	±	0	0	9	2	2	1	1	1	0	0	0	0	0	
	3/ 2/17	0	0	0	2	1	1	1	1	1	0	0	0	0	0	
	3/16/17	0	0	Faint+	6	1	2	2	2	1	1	0	0	0	0	
	8/10/17	0	0	+	20	2	2	1	1	0	0	0	0	0	0	
109	10/ 4/16	+	0	+	12	0	0	0	0	0	0	0	0	0	0	
	11/ 7/16	0	....	0	1	0	1	1	1	0	0	0	0	0	0	
	12/14/16	....	....	0	4	1	1	1	1	1	1	0	0	0	0	
	2/ 6/17	0	0	....	....	1	1	1	0	0	0	0	0	0	0	
	3/11/17	0	0	0	3	1	1	1	0	0	0	0	0	0	0	
	4/11/17	±	+++	....	5	1	2	3	2	1	0	0	0	0	0	
	6/ 5/17	0	0	0	4	0	0	1	1	0	1	1	1	1	1	
	7/ 1/17	0	0	?	4	1	1	1	2	1	0	0	0	0	0	
	8/17/17	0	0	....	8	1	1	1	0	0	0	0	0	0	0	
110	8/ 9/17	0	0	0	3	1	2	2	1	0	0	0	0	0	0	
	8/12/17	0	....	0	7	1	1	1	2	0	0	0	0	0	0	
	9/30/17	0	0	0	3	1	2	2	2	2	1	0	0	0	0	
	11/ 3/17	±	0	0	5	0.5	1	2	1.5	0.5	0.5	0	0	0	0	
111	3/22/17	0	±	0	4	1	1	2	3	2	1	0	0	0	0	
112	3/ 1/17	++++	++	+	24	1	1	1	2	3	2	2	1	0	0	Chronic nephritis
113	6/ 1/17	0	++	++	10	1	1	1	1	1.5	2	3	1.5	1	0	Tumor of spinal cord
	6/ 5/17	....	+	+	6	5	5	3	3	4	3	3	1	1	0	
114	7/27/17	....	++	++	200	5	1	1	2	3	4	2	0	0	0	
	7/31/17	....	....	....	....	1	1	2	3	3	2	1	0	0	0	
	8/14/17	....	+++	....	....	1	1	3	4	2	2	1	0	0	0	
	10/17/17	....	+	....	....	1	1	1.5	2	1.5	1.5	0	0	0		

TABLE 2.—Cerebrospinal Syphilis—Twenty-Two Cases—(*Continued*)

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
115	1/24/17	++++	++	0	6	1 1 2 3 3 2 0 0 0 0	Tabes dorsalis(?); tertiary syphilis; progressive muscular atrophy
	2/ 1/17	++++	++	0	12	1 1 1 3 2 1 0 1 0 0	
	2/10/17	+++	++	+	14	1 2 3 4 3 1 1 0 0 0	
	2/24/17	+	0	+	....	1 1 2 3 2 1 0 0 0 0	
117	11/17/16	++++	....	0	5	1 1 1 2 3 2 2 1 1 0	Chronic rheumato-arthritis
	12/15/16	+++	+++	0	5	1 1 1 2 2 3 2 1 1 0	Previous treatment
118	1/31/17	....	+++	+	10	1 1 1 1 1 1 0 0 0 0	
119	1/ 4/17	0	++	0	6	1 1 1 3 4 3 2 0 0 0	
	2/28/17	....	....	0	3	1 1 2 3 3 3 2 1 0 0	
	5/13/17	0	....	....	....	3 1 3 3 4 3 2 1 0 0	
	11/ 9/17	0	++	0	4	1 1 1 0.50.50 0 0 0 0	
120	4/ 5/17	A.C.	A.C.	+	50	1 2 3 4 3 2 1 0 0 0	
121	7/11/17	0	0	0	8	1 2 3 2 2 0 0 0 0 0	
	7/25/17	0	0	0	12	1 2 2 3 1 0 0 0 0 0	
	8/ 7/17	0	0	+	15	1 2 2 2 1 0 0 0 0 0	
	11/28/17	0	0	0	3	2 2 2 1 0 0 0 0 0 0	
122	8/24/17	++++	++++	?	10	0 5 4 3 2 1.51 1 0 0	
	8/29/17	++++	++++	?	15	1 1 2 3 4 3 1 1 0 0	
	10/31/17	++++	++++	+	9	1 1.52 2 1.50 0 0 0 0	
	12/ 2/17	+++	++++	+	13	1 2 2 2 1.50.50.50 0 0	
123	3/22/17	0	++++	+	....	1 1 2 4 3 1 0 1 2 2	
	5/23/17	0	+++	0	9	5 4 1.53.53 3 1.51 0 0	
	7/31/17	....	....	Faint+	5	1 1 2 3 2 3 0 0 0 0	
	9/20/17	0	+	?	5	0.50.51 2 2 1 0 0 0 0	
124	9/25/16	....	....	....	....	0 0 0 0 0 0 0 0 0 0 0	
	10/24/16	0	....	+	3	0 0 0 0 0 0 0 0 0 0 0	
	11/22/16	....	....	+	18	1 1 1 1 1 1 0 0 0 0	
	1/ 2/17	+	0	0	5	0 0 0 0 0 0 0 0 0 0	
	4/ 3/17	+	0?	0	3	1 1 1 2 0 0 0 0 0 0	
	6/ 1/17	+	0	0	8	1 1 1 1 1 0 0 0 0 0	
	8/13/17	+	0	+	....	1 1 1 1 0 0 0 0 0 0	
	10/13/17	+	0	+	36	0.50.50.51 1 0 0 0 0 0	
	11/14/17	+	0	++	15	0 0 0 0 0 0 0 0 0 0	
125	11/17/17	±	++	++	9	1 1 1 1 1 0 0 0 0 0	
	11/28/17	0	++	....	8	1 2 2 2 1 0.50 0 0 0	
126	11/ 1/17	++++	0	+	30	0.50.50.50.50.50 0 0 0 0	
127	10/15/17	+?	+++	++++	11	1 1 1 1.51.52 0 0 0 0	Cerebral gumma; tertiary syphilis
	11/ 2/17	±	+++	++++	120	0.51 1.52 3 1.51.50 0 0	
	11/12/17	++++	+++	....	....	1 1.51.51.52 1.51 0 0 0	
	11/28/17	+++	+	....	....	1.52 2 2 1 0.50 0 0 0	

Paresis.—In the group clinically diagnosed as paresis, comprising 6 cases, the blood Wassermann was negative in 1, the spinal fluid Wassermann in 2, and the cells under 10 in 2 cases, while the gold curve was of the irritation type in 1 instance. In 2 cases the curve was of the syphilitic type, once with both Wassermann reactions positive and once with both negative, but the others gave the characteristic paretic high level for the left hand tubes.

TABLE 3.—General Paresis—Six Cases

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
203	9/16/16	++++	++++	+	6	4 4 3.5 2 1 1 1 0 0 0	Tertiary syphilis
	9/29/16	++++	++++	+	5	5 4 1 2 2 2 1.5 0 0	
	10/16/16	++++	++++	+	16	1.5 1 1.5 2 3 3 1.5 0 0	
	11/ 7/16	++++	++++	+	12	4 2 2 3 2 2 0 0 0 0	
	11/25/16	++++	++++	++	12	3 3 2 2 2 2 0 0 0 0	
	12/16/16	++++	++++	.....	.....	2 2 2 3 3 3 1 0 0 0	
	1/ 5/17	++++	++++	+	6	1 1 2 4 3 2 1 1 0 0	
	2/ 3/17	+++	++++	0	3	2 2 1 1 1 1 0 0 0 0	
	3/ 6/17	++++	+++	+	59	1 1 2 3 4 3 1 1 0 0	
	4/ 7/17	++++	++++	+	40	3 3 2 1 0 0 0 0 0 0	
	5/ 8/17	+++	+++	+	34	1 1 2 3 3 2 3 0 0 0	
	6/19/17	++	++	++	350	1 2 2 3 3 2 0 0 0 0	
204	1/ 9/17	±	0	0	6	1 1 1 1 1 0 0 0 0 0	
205	6/ 7/17	+++	++++	+	.....	5 3 3 4 4 3 3 1 1 0	
	6/21/17	+++	+++	+	7	5 5 3 4 4 1 1 0 1 0	
206	7/21/16	A. C.	++++	+	8	5 5 5 5 5 5 5 2 1.5 0	
	7/26/16	++++	++++	+	11	5 5 5 5 5 1.5 1 0 0 0	Previous treatment
	11/ 5/16	++++	++++	+	14	5 5 5 5 5 5 5 1.5 0	
	11/22/16	+++	++++	++	36	4 4 4 4 4 4 3.5 1.5 1 0	
207	11/16/16	0	0	+	15	1 1 1.5 1.5 1.5 1 0 0 0	Syphilitic aortitis with aortic and mitral regurgitation; cardiac hypertrophy
	11/20/16	.....	0	++	30	1 1 1 2 2 2 0 0 0 0	
208	9/26/16	+	+++	+	9	1 1 1.5 3 2 1.5 0 0 0	
	10/10/16	0	+++	0	12	1 1 1 1 1.5 1 0 0 0	
	12/ 8/16	±	+++	+?	12	1 2 3 3 3 2 2 0 0 0	
	1/10/17	0	0	0	6	1 1 1 2 1 1 0 0 0 0	

TABLE 4.—Tertiary Syphilis—Twenty-Two Cases

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
128	11/15/16	+	0	0	.....	1 1 1 2 2 1.5 1 0 0 0	Aortitis with aortic regurgitation; splenomegaly (syphilitic?); leukemia?
129	8/29/17	0	0	0	6	1 1 1 1 0 0 0 0 0 0	Intestinal intoxication
130	2/ 1/17	++++	0	+	17	1 1 1 2 3 2 1 0 0 0	Cervical fibroid, pedunculated
131	11/ 3/16	++++	0	0	3	1 1.5 1.5 1.5 1 0 0 0 0 0	
132	1/25/17	++++	0	0	9	1 1 2 2 1 1 0 0 0 0	Optic neuritis
133	6/ 1/17	++++	++++	++++	42	2 2 5 3 3 3 1 1 0 0	Spastic paraplegia
	6/ 5/17	+++	+++	.....	.....	2 3 3 2 2 1 0 0 0 0	
	6/14/17	+++	+++	.....	.....	1 2 2 3 1 1 0 0 0 0	
	7/22/17	+	+	0	7	1 1 1 1 0 0 0 0 0 0	
	8/15/17	±	+	.....	.....	1 1 2 1 0 0 0 0 0 0	
134	4/ 5/17	.....	0	+	10	1 2 3 4 3 2 1 0 0 0	
135	12/ 3/16	0	+?	+?	7	1 1 2 2 2 2 1 0 0 0	Previous treatment
	2/10/17	0	++	0	5	1 2 2 3 3 1 0 0 0 0	
	8/20/17	0	.....	.....	.....	1 1 1 2 1 0 0 0 0 0	
136	11/ 4/16	+++	0	0	8	1 1.5 2 2 0 0 0 0 0	Pulmonary tuberculosis, chronic gumma of brain
137	12/ 9/16	++++	0	++	13	1 1 1 2 2 2 1 0 0 0	
	12/17/16	.....	0?	+	2	1 1 1 1 2 2 1 0 0 0	
138	10/13/16	+	0	0	3	1 1 1 1.5 1.5 1 0 0 0 0	Syphilitic hepatitis (gumma?); pelvic laceration
139	9/22/17	++++	0	?	8	0.5 0.5 0.5 0.5 0 0 0 0 0 0	
140	11/ 9/16	++++	0	0	2	1 1 1 1 1 0 0 0 0 0	
	3/18/17	++++	0	0	8	1 1 1 2 1 0 0 0 0 0	
	7/ 9/17	++++	0	0	1	1 1 1 1 1 0 0 0 0 0	
141	7/26/17	+	+	+	10	1 1 2 2 2 1 0 0 0 0	
142	11/16/16	+	0	+	20	1 1 1 1 0 0 0 0 0 0	
143	1/19/17	++++	0	0	8	1 1 1 1 1 0 0 0 0 0	Aneurysm of aorta (arch)
144	10/25/16	+	0	0	3	1 1 1 1.5 1.5 1.5 1.5 0 0	Syphilitic aortitis; chronic endocarditis; salvarsan poisoning
145	12/ 2/16	0	.....	+	7	1 1 1 2 2 1 0 0 0 0	"Salvarsan arm"
146	11/18/16	++++	0	.....	.....	1 1 1 1 1 0 0 2 0 0	
148	10/30/17	+++	0	0	2	1 1 1 1 0 0 0 0 0 0	Cholelithiasis?
149	9/10/17	+	0	0	7	1 1 1.5 1.5 1 0 0 0 0 0	
150	1/23/17	++++	0	.....	.....	1 1 1 1 1 1 1 0 0 0	

was positive in 16 cases, negative in 5 cases, and in another was not performed. The spinal fluid Wassermann was positive in 3 cases, was negative in 17, and was not performed in 2 cases. The globulin test was positive in 9 cases, negative in 10, and in 3 instances was not

made. The cells were 10 or under in 18 cases, and above 10 in 4 cases. The gold curve was in the syphilitic zone in 11 cases, and of the irritation type in 11. Of the 16 cases giving a positive blood Wassermann, 5 gave a negative spinal fluid Wassermann (Nos. 128, 130, 132, 136 and 137) but a gold curve in the syphilitic zone. In these 5 cases

TABLE 5.—Acute Anterior Poliomyelitis—Three Cases

Case No.	Date	Lymphocytes	Polynuclear Leukocytes	Globulin (Noguchi)*	Colloidal Gold Test
170	7/20/16	4	0	0	5 4 2 1 0 0 0 0 0 0
171	6/ 9/17	6	0	+	1 1 1 2 3 1 1 1 0 0
172	6/ 8/17	3	0	Faint +	1 1 2 1 0 0 0 0 0 0

* The Wassermann reactions on blood and spinal fluid were negative in every case.

TABLE 6.—Congenital Syphilis—Four Cases

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
173	8/29/17	.....	0*	0	4	1 1 1 1 1 0 0 0 0 0	
174	9/10/17	.....	0	?	8	1 1 1 1 0 0 0 0 0 0	
	11/11/17	++++	0?	0	4	0 0 0 0 0 0 0 0 0 0	
175	2/21/17	....	++++	+	30	1 1 2 2 1 0 0 0 0 0	
	3/15/17	++++	A. C.	+	9	1 2 3 2 1 1 0 0 0 0	
	5/27/17	+	±	+?	5	1 2 3 3 2 2 0 0 0 0	
	7/ 1/17	.....	0	0	4	1 2 3 2 1 1 0 0 0 0	
	9/23/17	.....	.....	0	4	1 1 1 0.5 0.5 0 0 0 0	
	10/27/17	.....	±	.....	5	1 1 1 1 0 0 0 0 0 0	
176	10/ 9/16	+	0	.....	.....	1 1 1 1 1 0 0 0 0 0	
	1/ 6/17	±	0	0	2	1 1 2 2 1 0 0 0 0 0	
	5/13/17	.....	0?	0	6	2 2 2 2 1 1 0 0 0 0	
	6/22/17	0	0	0	8	1 1 2 2 0 0 0 0 0 0	
	8/31/17	0	0	0	3	1 1 1.5 1.5 0 0 0 0 0	
	11/11/17	0	0	0	4	1 1 0 0 1 0 0 0 0 0	

* ++++ before treatment.

the globulin reaction was positive only twice. This indicates one of the most important uses of the gold reaction. It appears to be a more delicate index of syphilitic change in the spinal fluid than the Wassermann and the globulin test, and it is therefore of value in detecting the earliest onset of cerebrospinal lesions. The importance of this in the prophylaxis of the parasyphilitic diseases is evident,

TABLE 7.—Tuberculous Meningitis—Nine Cases

Case No.	Date	Lymphocytes	Polynuclear Leukocytes	Globulin* (Noguchi)	Colloidal Gold Reaction									Remarks
152	7/18/16	183	20	++	0	1.5	2	3	3.5	4	4	3.5	3	0	Pulmonary tuberculosis
	7/19/17	281	29	0	1	1	1.5	1.5	1.5	1.5	1	1	1.5	0	
	7/21/16	140	0	+++	1	5	4	1.5	1	0	0	0	0	0	
153	1/30/17	81	0	+	1	1	1	2	2	2	0	0	0	0	
154	8/ 6/17	30	1,470	+	1	1	2	2	1	0	0	0	0	0	
	8/ 9/17	90	210	+	4	1	3	2	1	0	0	0	0	0	
	8/10/17	324	486	+	1	1	1	1	2	3	1	3	0	0	
155	8/ 9/17	344	56	+	1	1	1	2	2	0	0	0	0	0	
156	12/ 5/16	171	9	++	1	1	2	2	2	2	1	1	0	0	
	12/ 6/17	393	12	++	1	1	1	1	2	2	2	1	0	0	
	12/10/16	182	15	++	1	1	1	2	3	3	2	1	0	0	
157	11/20/16	450	0	++++	1	1	1	1	2	3	3	3	0	0	
158	6/26/17	90	0	+	1	1	1	2	2	1	1	0	0	0	
159	6/29/17	88	0	+	1	1	1	1	3	3	1	2	0	0	
	7/ 2/17	98	0	+	1	2	1	3	3	4	2	2	0	0	
74	12/ 2/16	126	0	+	1	1	1	2	2	2	0	0	0	0	
	12/ 5/16	316	16	++	1	1	1	1	2	2	1	1	0	0	

* The Wassermann reaction was negative in every case in which it was performed.

TABLE 8.—Meningitis—Ten Cases

Case No.	Date	Lymphocytes	Polynuclear Leukocytes	Globulin* (Noguchi)	Colloidal Gold Test										Remarks
160	7/ 8/17	4	0	0	1	2	3	3	1	0	0	0	0	0	Serous meningitis
	7/16/17	4	0	0	1	1	2	2	2	1	0	0	0	0	
161	5/15/17	1,360	5,440	+	1	1	1	1	1	2	3	0	0	0	Epidemic cerebrospinal meningitis
162	5/15/17	440	660	+	0	0	0	0	1	1.5	0	0	1	1	Epidemic cerebrospinal meningitis
163	12/21/16	152	8	++	0	0	0	0	0	1	2	1	3	1	Lobar pneumonia; influenza
164	3/ 4/17	38	342	+	0	0	0	0	0	2	4	2	2	1	Pneumococcus meningitis, lobar pneumonia
165	4/24/17	140	1,260	+	0	0	0	0	0	0	0	1	1.5	2	Acute purulent meningitis (pneumococcus); ethmoiditis, purulent
166	5/28/17	3,750	8,750	+++	0	1.5	0	0	0	1.5	2	1.5	1		Epidemic cerebrospinal meningitis
167	11/17/16	267	513	++++	0	1	1	1	1	1	3	4	4	3	Septic meningitis (pneumococcus)
168	3/22/17	280	120	+	1	1	2	3	3	2	0	0	0	0	Cerebrospinal meningitis
	4/ 6/17	1,400	0	+	2	2	3	4	3	2	1	0	0	0	
169	1/22/17	64	1	+	1	1	1	2	1	0	0	0	0	0	Acute septic meningitis
	1/23/17	12	0	±	1	1	1	1	1	0	0	0	0	0	

* In every case in which the Wassermann reaction was performed it was negative.

and every syphilitic with a positive blood Wassermann should have the colloidal gold reaction done on the spinal fluid in order that proper treatment may be begun at a stage before permanent organic lesions have developed.

Three cases of poliomyelitis gave a pathologic gold curve in each instance, though the cells were below 10 in all three, and in one case the globulin reaction was negative. In one case the curve was in the paretic zone, and in the other two, it was of the syphilitic type.

Four cases of congenital syphilis are recorded. Of these, three gave positive blood Wassermanns, and one gave a positive spinal fluid Wassermann. Two of the cases gave a gold curve in the syphilitic zone, while two, both with negative spinal fluid Wassermann reactions, gave only irritation curves.

There are nine cases of tuberculous meningitis. These all gave curves chiefly in the syphilitic zone. Of ten other cases of non-tuberculous meningitis, all except one case of epidemic cerebrospinal meningitis gave curves which for the most part are characterized by a displacement to the right, which is typical of acute meningeal inflammation. One case is of interest because, although the cell count and the globulin reaction were both negative, so that the diagnosis of serous meningitis was made, the gold curve was a well marked one.

We have records of tests in 102 cases of miscellaneous conditions, in many of which pathologic curves were obtained, though not with sufficient regularity to be of definite diagnostic value. For example, of 12 cases of chronic nephritis, 7 gave only irritation curves, while in 4 cases accompanied by uremia, there was a well marked elevation in the syphilitic zone. In one of these the spinal fluid Wassermann was positive, though the cell count and globulin reaction were negative. In another case, there was complete flocking out of the gold in 7 of the 10 tubes. Of 5 cases of hysteria, 4 gave only irritation curves, but 1 with a positive globulin reaction and negative blood and spinal fluid Wassermann gave a syphilitic curve. Out of 3 cases of multiple sclerosis 1 was negative; another with positive blood and spinal fluid Wassermann, globulin reaction, and increased cell count gave first a syphilitic curve and ten days later a paretic curve. A third case in which the diagnosis was somewhat in doubt gave a syphilitic curve, though the blood and spinal fluid Wassermann, globulin, and cell count were all negative. In 2 cases diagnosed as neurasthenia there were curves in the syphilitic zone, though the blood and spinal fluid Wassermann, cell count, and globulin reaction were all negative, which is of interest as indicating a possible organic basis for the symptoms. One of the two cases of epilepsy gave a negative curve, and the other a syphilitic curve, though the other reactions were all negative. Three of the 4 cases of chorea gave negative curves, and the fourth a low

TABLE 9.—Miscellaneous Conditions—104 Cases

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Polynuclear Leucocytes	Colloidal Gold Test	Diagnosis
		Blood	Spinal Fluid					
6	4/16/17	0	+++	0	4	0	1 1 2 3 2 2 1 0 0 0	Chronic diffuse nephritis; uremia
9	8/ 7/17	0	0	0	3	0	1 1 1 2 1 0 0 0 0 0	Chronic nephritis; uremia; diabetes mellitus
12	10/24/16	0	0	0	3	0	1 1 1 1 1 0 0 0 0 0	Chronic diffuse nephritis; acute endocarditis; mitral insufficiency; right pleurisy with effusion
44	5/ 2/17	0	0	0	4	0	1 1 1 1 0 0 0 0 0 0	Chronic nephritis
49	7/30/17	0	0	....	....	....	1 1 1 1 2 3 3 1 0 0	Chronic nephritis; uremia; cystic adenoma of breast; colloid goiter; cerebral hemorrhage; fibroids of uterus
60	11/ 6/16	0	0	+	7	0	5 5 4 4 4 5 5 5 5 5	Chronic interstitial nephritis; cardiac hypertrophy; cerebral sclerosis; left hemiplegia
77	12/10/16	0	0	0	3	0	1 1 2 3 3 3 2 1 0 0	Chronic nephritis; arteriosclerosis; hypertension
78	2/16/17	±	0	0	5	0	1 1 1 1 0 0 0 0 0 0	Chronic nephritis; transitory uremia
88	5/26/17	0	0	0	6	0	1 1 1 1 1 0 0 0 0 0	Chronic nephritis; eczema
99	10/21/17	0	0	0	4	0	0.5 0.5 0.5 0.5 0 0 0 0 0 0	Chronic diffuse nephritis; hypertension; cardiac hypertrophy
100	11/14/17	++++	0	0	8	0	0.5 0.5 0.5 0.5 0.5 0 0 0 0	Nephritis; chronic endocarditis
103	10/30/17	0	0	....	....	....	1 1 1 1.5 0.5 0 0 0 0	Chronic nephritis; pulmonary tuberculosis
8	4/29/17	0	0	0	5	0	1 1 2 2 1 1 0 0 0 0	Hysteria
42	9/28/17	±	±	0	6	0	1 1.5 2 1.5 1 0 0 0 0 0	Hysteria
55	6/17/17	0	0	0	3	0	0 0 0 0 0 0 0 0 0 0	Hysteria
84	9/18/17	0	....	0	7	0	0.5 0.5 0.5 0 0 0 0 0 0 0	Hysteria
97	4/ 2/17	0	0	+	10	0	1 1 2 2 1 0 0 0 0 0	Hysteria
	4/14/17	0	....	....	10	0	1 1 1 2 2 1 0 0 0 0	
4	10/ 5/17	0	0	0	4	0	1 1,5 2.5 2.5 2 0 0 0 0 0	Multiple sclerosis ?
17	4/ 3/17	0	0	+	3	0	0 0 0 0 0 0 0 0 0 0	Migraine
30	9/ 6/17	0	0	0	3	0	1 1 1 1 1 0 0 0 0 0	Epilepsy
31	4/14/17	0	0	0	3	0	1 1 2 2 2 1 1 0 0 0	Neurasthenia
33	2/ 7/17	A.C.	0	0	6	0	1 1 2 3 3 2 0 0 0 0	Hematomyelia; transverse myelitis
	2/16/17	A.C.	0	+	17	0	3 1 3 2 3 4 3 2 0 0	
34	6/26/17	....	0	++	20	0	1 1 1 1 1 1 1 0 0 0	Polio-encephalitis
43	11/12/16	0	0	0	4	0	1 1 1 1 0 0 0 0 0 0	Chorea
	11/20/16	....	0	....	....	....	1 1 1 2 1 0 0 0 0 0	
48	10/ 6/17	0	0	0	....	....	1 1 1.5 1.5 1.5 0 0 0 0	Chorea
	10/16/17	....	0	0	6	0	0.5 0.5 0.5 0.5 0.5 0 0 0 0	
52	7/ 5/16	+	0	....	....	....	1.5 1 1 1 1 1 1 1 1 1	Transverse myelitis (syphilitic?)
61	7/26/17	0	0	?	7	0	1 1 1 1 0 0 0 0 0 0	Psychoneurosis
65	4/22/17	0	0	0	2	0	1 1 2 3 3 1 0 0 0 0	Neurasthenia; toxic neuritis
66	9/28/17	0?	0	0	3	0	1 1 1.5 1 0 0 0 0 0 0	Headache

TABLE 9.—MISCELLANEOUS CONDITIONS—104 CASES—(*Continued*)

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Polynuclear Leukocytes	Colloidal Gold Test										Diagnosis
		Blood	Spinal Fluid														
72	12/ 7/16	0	0	0	3	0	1	1	1	2	2	1	0	0	0	0	Chronic alcoholism with edema of brain; pleurisy with effusion; pulmonary tuberculosis
76	12/10/16	0	0	0	6	0	1	1	2	2	2	1	0	0	0	0	Sciatica
13	6/ 5/17	0	0	+	12	0	1	1	2	3	2	2	0	0	0	0	Alcoholic neuritis; delirium tremens
79	7/24/17	0	0	+	128	2	1	1	1	0	0	0	0	0	0	0	Chorea
	8/ 2/17	....	0	0	3	0	1	1	1	0	0	0	0	0	0	0	
80	6/16/17	0	0	....	....	....	1	1	1	2	2	0	0	0	0	0	Functional neurosis
81	11/ 3/16	0	0	0	4	0	1	1	1	1	1	1	0	0	0	0	Alcoholic neuritis
	11/ 7/16	....	....	0	3	0	1	1	1	1.5	1.5	0	0	0	0	0	
	11/13/16	....	....	0	6	0	1	1	1	1	0	0	0	0	0	0	
82	7/27/17	0	0	?	10	0	1	1	1	2	1	1	0	0	0	0	Paralysis due to toxic agent
86	10/17/16	....	....	0	6	0	0	0	0	0	0	0	0	0	0	0	Chronic chorea
	11/14/17	....	...	....	6	0	1	1	1	0	0	0	0	0	0	0	
94	7/15/17	0	0	0	4	0	1	1	1	1	1	0	0	0	0	0	Traumatic neurosis
101	11/15/17	+++	+++	++	23	0	1	1.5	3	2	1.5	0.5	0	0	0	0	Multiple sclerosis
	11/25/17	+++	+++	++	13	0	5	5	4	3	2.5	2	1	0	0	0	
102	11/17/17	0	0	+++	7	0	0	0	0	0	0	0	0	0	0	0	Multiple sclerosis?
7	6/29/17	0	0	+	6	0	1	1	1	1	2	2	2	1	0	0	Cerebral tumor
5	1/18/17	0	0	....	....	....	1	1	1	1	2	2	1	0	0	0	Cerebral hemorrhage; glaucoma
23	5/14/17	....	0	0	3	0	0	0	0	0	0	0	0	0	0	0	Hemiplegia
26	2/10/17	0	0	+	8	0	1	1	1	2	2	1	0	0	0	0	Hemiplegia
28	9/11/17	0	0	0	4	0	1.5	1	1	1	1	0	0	0	0	0	Hemiplegia
36	6/23/17	0	0	+	4	0	0	0	0	0	0	0	0	0	0	0	Partial left hemiplegia; multiple cerebral softening
93	1/15/17	0	0	+	108	0	1	1	1	2	2	1	0	0	0	0	Hemiplegia
50	10/ 3/17	0	0	0	5	0	0.5	1	1	1	0	0	0	0	0	0	Spastic paraplegia (lateral sclerosis?); secondary anemia
63	4/ 1/17	0	0	0	....	....	1	1	1	1	0	0	0	0	0	0	Neuralgia of fifth facial nerve
90	3/30/17	0	0	0	6	0	1	1	2	2	1	0	0	0	0	0	Epilepsy; Pott's disease
32	11/14/16	0	0	+	8	0	1	1	1	1	1	1	1	0	0	0	Chronic alcoholism
40	6/11/17	0	0	0	4	0	1	1	1	1	1	0	0	0	0	0	Alcoholic neuritis
70	11/24/16	0	0	+	15	0	1	1	1	2	2	2	1	0	0	0	Brain tumor
	11/30/16	0	0	....	....	....	1	1	1	2	2	2	1	0	0	0	
	12/ 7/16	0	0	+	9	0	1	1	1	2	2	2	1	0	0	0	
	12/10/16	0	0	++	32	0	1	1	1	2	2	3	1	0	0	0	
	12/21/16	0	0	+	15	0	1	1	1	2	3	2	1	1	0	0	
	1/ 3/17	0	0	0	6	0	1	1	1	2	2	2	3	2	0	0	
10	1/ 8/17	0	0	0	5	0	1	1	1	2	2	1	0	0	0	0	Chronic myocarditis

TABLE 9.—Miscellaneous Conditions—104 Cases—(*Continued*)

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Polynuclear Leukocytes	Colloidal Gold Test	Diagnosis
		Blood	Spinal Fluid					
19	5/21/17	0	0	0	3	0	1 1 2 3 2 1 1 0 0 0	Aortic aneurysm
21	10/10/17	0	....	0	5	0	1 1 1 1.5 1 0 0 0 0	Chronic myocarditis
37	8/ 7/17	0	0	0	4	0	0 0 0 0 0 0 0 0 0 0	Chronic endocarditis; chorea
41	9/10/17	++++	0	0	6	0	0 0 0 0 0 0 0 0 0 0	Chronic endocarditis
45	7/27/17	0	0	0	8	0	1 1 1 0 0 0 0 0 0 0	Chronic cardiac valvular disease; chronic cardiac insufficiency; chronic dilatation; aortitis; manic depressive psychosis
57	10/ 8/17	0	0	0	5	0	1 1 1 1.5 1.5 1.5 0 0 0	Endocarditis
62	7/19/17	0	0	0	2	0	0 0 0 0 0 0 0 0 0 0	Aortic aneurysm of arch; arteriosclerosis and hypertension
87	5/28/17	++++	0	0	2	0	1 1 2 2 3 2 1 0 0 0	Aortic aneurysm; celiac axis aneurysm
89	5/30/17	0	0	0	16	0	1 2 3 2 2 1 0 0 0 0	Paroxysmal tachycardia
18	5/22/17	....	0	0	10	0	1 1 1 2 1 0 0 0 0 0	Lobar pneumonia
29	2/ 1/17	0	0	0	12	0	1 1 1 1 1 1 0 0 0 0	Lobar pneumonia
	2/ 2/17	0	0	0	8	0	0 0 0 0 0 0 0 0 0 0	
	2/ 4/17	....	....	0	5	0	1 1 1 1 0 0 0 0 0 0	
69	4/13/17	....	....	0	5	0	1 1 2 2 2 2 0 0 0 0	Lobar pneumonia
92	6/23/17	0	0	+	45	0	0 0 0 0 0 0 0 0 0 0	Lobar pneumonia
38	5/11/17	....	0	0	4	0	1 1 1 1 0 0 0 0 0 0	Bronchopneumonia; otitis media
14	6/ 9/17	0	....	+	10	0	1 2 2 1 0 0 0 0 0 0	Acute bronchitis; chronic emphysema
75	11/ 8/16	0	0	0	7	0	1 1.5 2 2 1.5 1.5 0 0 0	Acute miliary tuberculosis
1	1/22/17	0	....	0	4	0	1 2 2 2 0 0 0 0 0 0	Phimosis; mental deficiency
2	7/ 7/17	0	0	0	4	0	1 2 2 3 1 1 0 0 0 0	Intestinal intoxication; arteriosclerosis; hypertension; pyelitis; aortitis
3	1/30/17	0	0	0	3	0	0 0 0 0 0 0 0 0 0 0	Chronic iritis
11	2/26/17	0	....	0	3	0	1 1 1 2 1 1 1 0 0 0	Acromegaly
15	8/27/17	0	0	0	7	0	2 2 1 1 0 0 0 0 0 0	Acute gastro-enteritis
16	12/15/16	0	....	....	....	....	1 1 1 1 1 1 3 1 0 0	Hydrocephalus
20	4/16/17	0	0	+	2	0	1 1 2 1 0 0 0 0 0 0	Recurrent carcinoma of uterus; pelvic and spinal (?) metastases
22	3/11/17	0	0	0	5	0	1 1 1 1 1 0 0 0 0 0	Goldthwaite's disease; subluxation of sacroiliac joint
24	1/11/17	0	0	0	3	0	1 1 1 2 1 1 0 0 0 0	Hypertension
25	2/28/17	....	0	0	5	0	0 0 0 0 0 0 0 0 0 0	Uveitis; posterior synechiae; panophthalmitis; neurasthenia
27	3/26/17	0	0	+?	....	0	1 1 1 2 3 0 0 0 0 0	Ischiorectal abscess
35	10/29/16	0	0	0	1	0	1 1 1 1.5 1.5 0 0 0 0	Menopause
39	6/13/17	0	0	+	4	0	1 1 1 1 0 0 0 0 0 0	Tumor of right brachial artery

TABLE 9.—Miscellaneous Conditions—104 Cases—(*Continued*)

Case No.	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Polynuclear Leukocytes	Colloidal Gold Test										Diagnosis
		Blood	Spinal Fluid														
46	5/28/17	0	0	....	20	0	**1**	**1**	**1**	**2**	**0**	**0**	**0**	**0**	**0**	**0**	Iliac thrombosis; pelvic tumor?
	8/15/17	....	0	....	....	....	1	1	1	0	0	0	0	0	0	0	
47	9/22/17	0	0	0	3	0	0.5	0.5	0.5	0.5	0	0	0	0	0	0	Gastric neurosis and flatulence; gonorrheal cervicitis
51	1/26/17	0	0	0	6	0	1	1	1	1	0	0	0	0	0	2	Chronic gastritis
53	11/30/16	0	0	0	9	0	1	1	1	1	1	0	0	0	0	0	Retroversion; fibroid (?), uterus
54	5/21/17	0	0	....	2	0	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**0**	**0**	**0**	Chronic septic arthritis, hip
56	10/10/16	0	0	++	8	0	0	0	0	1	1	0	0	0	0	0	Endarteritis (syphilitic ?) spinal cord
58	10/19/16	....	0	+++	20	0	**0**	**0**	**0**	**0**	1	1	1.5	1.5	1	0	Sarcoma, right popliteal region; spinal cord metastasis
59	12/16/16	0	0	0	3	0	1	1	2	2	2	2	1	0	0	0	Gastric ulcer
	6/29/17	0	0	....	....	....	1	1	1	2	1	1	2	**0**	**0**	**0**	
64	7/13/17	0	0	0	3	0	**1**	**2**	**2**	**1**	**0**	**0**	**0**	**0**	0	0	Chronic cholecystitis
67	7/ 9/17	0	0	+	6	0	1	1	2	3	2	0	0	0	0	0	Acute epididymitis
68	10/15/16	0	0	0	3	0	1	1	1	1.5	1.5	0	0	0	0	0	Carcinoma of stomach
71	3/21/17	....	....	+	10	0	**1**	**1**	**1**	**1**	**1**	**1**	**1**	0	0	0	Congenital polycystic kidneys; acute uremia
73	10/25/16	0	0	....	8	0	0	0	1	1.5	1.5	1.5	0	0	0	0	Splenomegaly
	11/ 7/17	0	0	....	1	1	1	1	1.5	2	2	1.5	1	0	0	0	
	11/13/16	+	0	+	8	0	1	1	1	1.5	2	1.5	1	0	0	0	
	11/16/16	0	0	+	21	4	**1**	**1**	**1**	1.5	2	2	2	1	1	0	
	11/29/16	0	0	+	15	0	1	1	1	2	3	3	1	0	0	0	
	1/30/17	....	0	+	3	0	1	1	1	1	1	1	0	0	0	0	
83	8/23/17	0	....	0	3	0	1	1	1	0	0	0	0	0	0	0	Acute enteritis
85	2/22/17	....	0	+	4	8	1	1	1	1	0	0	0	0	0	0	Fractures, base of skull, and leg
91	10/ 8/17	....	0	0	3	0	0	1	1.5	1.5	1	0	0	0	0	0	Duodenal ulcer
95	7/ 7/17	++++	0	+	6	0	1	1	2	1	0	0	0	0	0	0	Acute rheumatic fever
96	9/25/16	0	0	0	4	0	**0**	**0**	**0**	**0**	0	0	0	0	0	0	Chronic otitis media; epilepsy (?)
98	10/ 5/17	0?	0	0	4	0	1	2	2.5	3	1	0	0	0	0	0	Carcinoma of liver
104	10/31/17	0	0	+	7	0	0.5	0.5	0.5	1	1	0.5	0	0	0	0	Chronic infective arthritis

syphilitic curve, the other tests being negative. One case of transverse myelitis gave only an irritation curve, and another a syphilitic curve, the other tests being negative. There were 5 cases of chronic alcoholism. Two of these, one in which the diagnosis of edema of the brain was made, and the other with delirium tremens, gave syphilitic curves, though the Wassermann reactions were negative, but 3 cases with peripheral neuritis gave only irritation curves. Two cases of brain tumor with positive globulin reactions, but negative Wassermann reactions, gave curves showing a slight displacement to the right. Of 5 cases of hemiplegia, 3 gave negative curves and 2 syphilitic

curves, though the Wassermann tests were negative. A curious observation was that in a case of paroxysmal tachycardia there were 16 cells per cubic millimeter and the gold curve was in the syphilitic zone, though the Wassermanns were negative.

In comparing the gold curve and the spinal fluid Wassermann the following may be said: In our series comprising 24 cases of tabes, 22 of cerebrospinal syphilis, 22 of tertiary syphilis, 6 of general paresis and 4 of congenital syphilis, or 78 altogether, there were no instances in which at the first examination the spinal fluid Wassermann was positive but the gold curve was negative. There were two cases, however, in which the spinal fluid Wassermann was positive and the curve was under two in the scale at the first examination. These were both cases of cerebrospinal syphilis, and in one (No. 118) only a single examination was made, but in the other (No. 125), although the first examination gave a curve under two, a later one showed a good syphilitic reaction.

On the other hand, in these 78 cases there were 33 in which at the first examination the spinal fluid Wassermann was negative, but the gold curve was pathologic in character. In 16 of these cases the curve reached 2 or over in the scale, and it is particularly interesting to note that 7 of these instances occurred in cases of tabes.

CONCLUSIONS

1. It must be emphasized that each of the different tests on the spinal fluid is of value only as a single factor in the entire examination, and that no one test alone is pathognomonic.

2. The colloidal gold reaction is the most sensitive indicator we have of pathologic changes in the spinal fluid, the globulin reaction closely approaching it in delicacy.

3. Uremia, neurasthenia, serous meningitis, hemiplegia and chronic alcoholism may give a curve in the syphilitic zone.

4. If the gold reaction is negative, it is highly probable that the spinal fluid Wassermann will also be negative.

5. An important application of the gold reaction is in the recognition of the earliest stages of cerebrospinal syphilis, and its routine employment in all syphilitics is to be recommended as an aid in the prophylaxis of the parasyphilitic diseases.

680 Madison Avenue.

A CLINICAL STUDY OF ONE HUNDRED AND FIFTY CASES OF BRONCHIAL ASTHMA*

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Within the past few years, there has been a growing interest in the association and relation between anaphylaxis and asthma. The original theories of this relation have been often discussed.

This growing interest has served to emphasize the important point that the diagnosis of bronchial asthma is only the first step in the diagnosis of the absolute cause of the particular patient's difficulty.

The writer's purpose in this present work has been to determine the cause of asthma in the 150 patients who form the basis of this report and, if possible, to arrange these patients in groups. These 150 patients were seen in the out-patient department and wards of the Massachusetts General Hospital, and a few outside the hospital.

Each patient had been previously studied by a competent internist. Organic lesions of the heart, lungs and blood as a cause of dyspnea, had been considered and ruled out, often only after sputum examinations and roentgen-ray examinations of the chest had been made.

Each patient gave a history of attacks of shortness of breath accompanied by wheezy respiration, for which attacks no obvious cause could be found by the ordinary clinical examination.

In each case, the diagnosis of asthma had been made previously, and on this account the patient was referred to the writer. Such diagnoses were accepted without further study.

ETIOLOGIC FACTORS

The prevalent and generally accepted theory today is, as Meltzer[1] originally pointed out, that asthma is a clinical manifestation of anaphylaxis; that these patients with asthma are sensitized to various foreign proteins which are either inspired or ingested from without the body or absorbed from some focus of infection or suppuration within the body. The cases in this report have been studied in the light of this theory.

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* From the medical service of the Massachusetts General Hospital, Boston.

1. Meltzer, S. J.: Anaphylaxis and Asthma, Jour. Am. Med. Assn., 1910, **55**, 1021.

The medical literature of recent years is full of attempts to find the cause of asthma. The work of Walker is especially brilliant and the reader is referred to his original papers,[2] and to his excellent summary[3] for full details.

Asthma from inhalations of horse hair,[2] plant pollens,[2] feather dust,[2] etc.; from eating of eggs,[4] berries,[5] fish,[6] cereals,[7] etc., are all known, and such cases will be referred to in the present paper as having an extrinsic cause of their asthma. Intrinsic causes are also well recognized, that is, where the cause lies within the patient's body. For example, there is much literature dealing with the relation of pathologic conditions in the nose and throat to asthma.

Grant[8] summarizes the findings in his 107 cases, and records improvement or cures of asthma in forty-five out of fifty-nine cases treated for nasal disease. Abbott,[9] Gottlieb[10] and Bonnier[11] all consider the nose and throat and local treatment directed to it, as being important. Matthews[12] from the Mayo Clinic says that in over 90 per cent. of the cases the principal etiologic lesions are in the upper respiratory tracts; and that treatment is successful in proportion as free and continuous drainage is obtained.

The cases of Davies[13] illustrate other intrinsic causes: where the asthma was apparently relieved by the appropriate treatment of such conditions as uterine displacement, undescended testicle, abdominal ptosis, constipation, dysmenorrhea, etc., and where, because of this relief, the author claimed an etiologic relationship between these conditions and the asthma.

Hare[14] has seen asthma associated with malaria, migraine, epilepsy, Raynaud's disease, etc.

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2. Walker, I. C.: Studies in Bronchial Asthma, Jour. Med. Research, 1917, **31,** 243.
3. Walker, I. C.: Studies on the Cause and the Treatment of Bronchial Asthma, Jour. Am. Med. Assn., 1917, **69,** 363.
4. Schloss, O. M.: Am. Jour. Dis. Child., 1912, **14,** 341.
5. Frost, L. C.: A Case of Intense Food Anaphylaxis, Med. Rec., New York, 1915, **88,** 483.
6. Muhsam and Jacobson: Deutsch. med. Wchnschr., 1914, **40,** 1067.
7. Smith, H. R.: The Archives Int. Med., 1909, **3,** 350.
8. Grant, Dundes: Nasal Disease in Relation to Asthma, Practitioner, Lond., 1913, **90,** 914.
9. Abbott, W. J.: Bronchial Asthma and the Relation of Nasal Conditions to It, Am. Jour. Otol., Rhin. and Laryngol., 1914, **33,** 83.
10. Gottlieb: Etiology and Treatment of Bronchial Asthma, New York Med. Jour., 1917, **106,** 313.
11. Bonnier: Arch. gén. de méd., Paris, **91,** 197.
12. Matthews, J.: Med. Rec., New York, 1914, **84,** 507.
13. Davies, B. C.: A Clinical Study of Asthma, Jour. Am. Med. Assn., 1914, **62,** 1006.
14. Hare, F.: Varieties and Treatment of Asthma, Brit. Med. Jour., 1911, **2,** 1442.

Babcock's case[15] is also interesting in which the asthmatic attacks were definitely related to cessation of drainage from an infected gall-bladder.

Jackson[16] has distinguished two types of experimental asthma; (1) that due to stimulation of the broncho-constricting muscles directly, and (2) the type due to the stimulation of the nerves to these muscles. He does not indicate more remote causes or attempt to group cases, his work being done entirely with animals.

It is worth while here to review briefly some of the facts of experimental anaphylaxis. A sensitized guinea-pig will react always to a parenteral introduction of the protein or proteins to which he is sensitized; this reaction being either local or general according to the dose and method of administration. He will not react to other proteins; the reaction is thus highly specific. The reaction takes place at once and its intensity varies with the size of the reinjection dose. In case of recovery, the guinea-pig will not again react to the same foreign protein until after a certain latent period.

When, on the other hand, we come to study critically many cases of asthma, we find that most of these well recognized postulates of experimental anaphylaxis do not obtain. But there are certain obvious differences.

In the first place, we are dealing with man and not animals. In the second place, we are dealing with cases of natural sensitization and, as Dr. Longcope[17] has pointed out, there are many differences between this and artificial sensitization, for as he showed, in naturally sensitive men, the susceptibility is very great, reactions often of violent character being readily produced by minute quantities of the particular proteid; the susceptibility is often shown toward several proteins at once and is, therefore, multiple; and finally, natural sensitiveness has a tendency to occur in families.

One method of demonstrating this sensitiveness or susceptibility is by the use of the skin test.

The fact that persons who are sensitive to proteins give a local reaction to the application of that protein in the skin was brought out as long ago as 1910 by Moss,[18] who also found[19] that artificially sensi-

15. Babcock, R. H.: The Nature and Treatment of Bronchial Asthma, Jour. Am. Med. Assn., 1915, **64,** 2115.

16. Jackson, D. E.: Pharmacology of Bronchial Asthma, Jour. Lab. and Clin. Med., 1915, **1,** 126.

17. Longcope, W. T.: Susceptibility of Man to Foreign Proteins, Am. Jour. Med. Sc., 1916, **152,** 625.

18. Moss: Jour. Am. Med. Assn., 1910, **55,** 776.

19. Knox, Moss and Brown: Subcutaneous Reactions of Rabbits to Horse Serum, Jour. Exper. Med., 1910, **12,** 562.

tized rabbits develop a positive skin test to the original protein after an incubation period of from seven to ten days.

Since then, and especially in recent years, the skin test has had wide usage, when its application to the diagnosis of hay fever, horse asthma and many other conditions thought to be dependent on an anaphylactic background has been frequent and usually satisfactory.

SCOPE OF THIS REPORT

The cases in this report are essentially adults; more than half of them began to have asthma when they were past the age of 20.

The individual cases in this report have been studied as follows: A careful history has been obtained in each case, the particular object being to discover the conditions and circumstances related to the attacks of asthma.

A complete physical examination has been made, including in most cases an examination of the nose and throat by an expert, and in many cases a roentgenogram of the chest.

Skin tests have been studied in nearly all the patients. In this work the intradermal method, by which definite amounts of protein are injected between the layers of the skin, has been used exclusively. The proteins used have been various animal serums; solutions of egg-white and extracts of plant pollens, of animal hairs, and of fish muscle, different combinations being used according to the history and findings in the individual cases. These protein solutions were all standardized according to their total nitrogen content, were sterile, and gave no reaction in the skin of normal control individuals.

In the performance of these tests, each protein except the various animal serums, was diluted with 0.9 per cent. salt solution containing 0.5 per cent. carbolic acid, so that each cubic centimeter of the resulting solution contained 0.02 mg. of total nitrogen. In this way it has been possible to compare the various local reactions one with another in as accurate a way as possible. The animal serums were each diluted 1 : 100.

The tests have invariably been performed on the outer aspect of the upper arm beginning at the tip of the olecranon process. The 0.25 c.c. pipet-syringes described by Terry[20] have been found very convenient for making the intradermal injections, as they can be sterilized by dry heat, are then ready for instant use, and can be easily transported. An injection of carbolized salt solution was always given as a control.

The typical positive reaction consists of an urticarial wheal which appears usually within five minutes and within fifteen minutes reaches often from 12 to 16 mm. and occasionally from 50 to 60 mm. in

20. Terry, M. C.: Precision Syringes, Jour. Infect. Dis., 1913, **13**, 80.

diameter. It has sharply defined, steep borders. Very characteristic are the pseudopodia-like projections which extend out in all directions making very grotesque figures. A bright pink areola with fairly sharp border is almost always present, but the criterion of a positive test has been the enlarging wheal and not this areola.

In many cases, in which a series of tests have been done, the arm will present a row of elevated macules each measuring from 8 to 12 mm. with a relatively small well defined and often mottled areola around each, the areola measuring, perhaps, from 15 to 30 mm.—the test with plain carbolized salt solution giving the same appearance. There are no pseudopodia and the wheal does not enlarge as fast as does the areola. Such results have been interpreted as showing that the skin of that particular person was such that any test solution might act purely as an irritant. Such tests have obviously been discounted in the diagnosis.

More rarely, perhaps only a half of the test solutions showed this "irritative" reaction; these reactions have been all discounted.

It should be said that there are often all transitions between the true "anaphylactic" reactions and these irritative reactions, and that the differentiation and interpretation is often difficult. The cases of definite susceptibility, however, almost never fail to give a true reaction to the specific protein.

Great stress has been laid on these skin tests only when results obtained were compatible with the patient's history. For example, if a patient gave a positive skin test to ragweed pollen extract and yet had asthma throughout the year, the test was more or less disregarded unless it so happened that there was a definite aggravation of symptoms during the hay fever season.

Skin tests were done on a total of 127 out of 150 cases. One or more tests were positive in 74 cases (50 per cent.), and of these 74 positive tests, 40 (in 27 per cent. of the cases) were compatible with the patient's history, and under these conditions the diagnosis, or at least one factor in the diagnosis, was assumed to be proved.

In this way these cases have been arranged in groups.

Effort has been made to keep in touch with as many patients as possible, to see if the course of their asthma proved to be consistent with the original impression and classification of the case.

Before considering the individual groups, it should be noted that asthmatic individuals fall into two great divisions according to whether their asthma depends on the susceptibility to foreign proteins without the body (extrinsic), or whether their asthma depends on the theoretical absorption of foreign, in this case probably bacterial, protein from within the body (intrinsic).

DIFFERENTIATION OF CASES

In order to aid in the differentiation between extrinsic and intrinsic cases, stress has been laid on three special points:

(1) *On the Family History.*—Longcope in particular has brought out the hereditary tendency of natural sensitiveness. Cooke[21] found in his 621 cases of sensitization a positive family history on one side in 205 cases, and a positive on both sides in 39 cases; or a positive family history in 48 per cent. of his cases of hay fever, which, as he says, is in striking contrast to the 14.5 per cent. of positive antecedent histories in seventy-six normal persons.

Talbot[22] finds a positive family history in all of the 19 cases of asthma in children which he studied in great detail. The fact that patients with asthma or hay fever are more likely to recognize similar disease in their relatives than people not suffering from this disease is obvious.

It should here be said that most of the cases in this report are from the out-patient class, and as such do not often give competent answers. Furthermore, they have asthma. The relation of family history to different groups of asthma will be discussed later.

(2) *On the Eosinophilia.*—It is known that foreign protein acts as an eosinotactic substance while bacteria seem to repel the eosinophil cells (Staubli[23]).

Furthermore, according to the Ehrlich-Lazarus conception,[24] eosinophilia occurs whenever epithelial or cellular destruction goes on, and as Schlecht says, it is of favorable significance insofar as it is an expression of a reaction from foreign protein that has entered the body, or from native protein abnormally broken up inside the body.

Eosinophilia can be artificially produced in animals by the injection of foreign protein substances (Staubli,[25] Schlecht[26] and Pröscher[27]).

And in man, after an injection of diphtheria antitoxin, there is a rise of eosinophils, which rise depends on the amount of serum injected (Schlecht[27]).

If a sensitized animal is reinjected, there is at first a local eosino-

21. Cooke, R. A., and Vander Veer: Human Sensitization, Jour. Immunol., 1916, **1,** 201.
22. Talbot, F. B.: Asthma in Children, Etc., Boston Med. and Surg. Jour., 1916, **175,** 191.
23. Staubli: Trichiniasis, J. F. Bergman, Wiesbaden, 1909.
24. Schlecht, Heinrich: Arch. f. exper. Path. u. Pharmakol., 1912, **67,** 137.
25. Staubli, Carl: Ergebnisse der Inn. Med. v. Kinderheilkunde, 1910, **6,** 193.
26. Pröscher: Folia Haemat., 1905, **2,** 543.
27. Schlecht, Heinrich: Deutsch. Arch. f. inn. Med., 1912, **98,** 327.

philia at the point of reinjection, and later a general increase in the number of these cells (Schlecht and Schwenker[28]).

On account of these many past observations, it was anticipated that the finding of an eosinophilia might indicate an extrinsic cause of asthma, and also that it might indicate resistance to the foreign protein responsible. As will be shown in the following, these hypotheses have not been substantiated by the present work.

(3) *On Treatment.*—This latter point needs further comment. It is known that ordinary hay fever can be much alleviated by repeated parenteral injections of the particular pollen extract to which the patient is sensitive (Cooke,[29] Goodale,[30] and others). Horse asthma also can be successfully treated with horse hair protein (Goodale,[30] Cooke,[31] Walker[32]), and Schloss[4] treated his egg sensitive baby with small and repeated doses of egg-white.

Having made a tentative diagnosis of the kind of asthma in these patients, a good check on this diagnosis has been the result of specific treatment. Thus, treatment often has a bearing on the diagnosis.

The treatment of asthma by repeated injections of the patient's own blood defibrinated, was suggested by Kahn and Emsheimer.[33] It has been tried in three patients but with no permanent result.

The groups under the division of extrinsic asthma include pollen asthma, horse asthma and acute food asthma.

POLLEN ASTHMA

Twenty-four cases gave a definite history of aggravation of asthma during the summer months, and all but five gave a positive skin test to extracts of one or more pollens. They are, therefore, grouped together. It seems reasonable to assume that these individuals are all susceptible to plant pollen. This susceptibility is a highly specific one. The onset date of the autumn asthma is, in several histories, almost exactly coincident with the onset date of many cases of simple uncomplicated hay fever, and in about half of twenty-four cases the asthma ceases abruptly with the first frost. On these accounts, we may say that anaphylaxis in the strict sense plays an important part in these cases and that in twelve of them it is the only factor.

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28. Schlecht and Schwenker: Deutsch. Arch. f. klin. Med., 1912, **108,** 405.
29. Cooke, R. A.: Treatment of Hay Fever, Laryngoscope, 1915.
30. Goodale, J. L.: Vasomotor Disturbances of the Upper Air Passages, Boston Med. and Surg. Jour., 1916, **175,** 181.
31. Cooke, R. A.: Personal Communication.
32. Walker, I. C.: Jour. Med. Research, 1917, **35,** 497.
33. Kahn and Emsheimer: The Archives Int. Med., 1916, **18,** 445.

However, in the other twelve there must be another factor, because these twelve cases have asthma at other times as well, the cause of which is in most cases a mystery.

The five patients who failed to give a positive skin test to one or more of the pollens are detailed in the following reports (refer to Table 1):

TABLE 1.—POLLEN ASTHMA. TWENTY-FOUR CASES

Case No.	Sex*	Present Age	Age at Onset	Hay Fever	Skin Tests to Pollens	Asthma Worse in Summer	Asthma at Other Times	Treatment With Pollen Extracts	Family History	Eosinophilia, per Cent.	
										In Attacks	Between Attacks
8	♂	22	5	+	+	+	0	++	+		
16	♂	26	24	+	+	+	0	.....	0		
21	♀	6	4	0	+	+	0	.....	+	0	5.6
22	♀	48	30	+	+	+	0	++	+	.....	1.6
36	♂	12	6	0	0	+	0	.....	0		
53	♀	38	34	+	+	+	0	.....	0	.....	2
62	♀	11	9	0	+	+	0	.....	0	12	5
106	♂	46	31	+	+	+	0	+++	.....	.....	0.3, 0.3
116	♂	31	21	+	+	+	0	++	+		
126	♀	28	28	0	+	+	0	.....	.....	2	
135	♂	54	37	0	0	+	0				
143	♂	3	1	+	+	+	0	.....	+		
2	♀	23	19	+	0	+	+	b	+	9.3, 9.3	2.6
3	♀	51	50	+	0	+	+	.....	0	4	10
10	♂	55	53	+	+	+	+	.....	.....	.....	2
12	♀	48	39	+	+	+	+	.....	+	4.6	8.3
14	♂	12	8	0	+	+	+	.....	.....	10	5
49	♂	35	30	+	+	+	+	±	0	3, 2.6	
77	♀	44	30	+	0	+	+	.....	+		
105	♀	25	16	+	+	+	+	.....	0	.....	3
110	♂	39	31	+	+	+	+	.....	.....	5.3	
112	♀	52	21	+	+	+	+	+	+	0	6.6
121	♀	36	26	0	+	+	+	.....	0	4, 5	10
135	♂	50	39	0	+	+	+	.....	0	.....	2.6

* ♂ = male; ♀ = female.

SUMMARY OF CASES

CASE 77.—This case is interesting because, although the patient gave no skin tests, she had a typical hay fever from July until frost, a positive family history, and during this hay fever often had urticaria.

CASE 135.—This patient is a hostler, aged 54, with asthma for seventeen years which comes on only in the autumn, usually late in August. In spite of a negative test to ragweed and no hay fever he is grouped here. He might very possibly give a test with some other of the compositae.

CASE 36.—A boy, aged 12, had asthma only during the summer. In spite of the fact that chest roentgenograms showed the presence of a large mediastinal gland, in spite of the negative skin tests and the absence of any history of hay fever, he is inserted in this group because in the winter he is perfectly well.

CASE 10.—Although this patient had had hay fever from August until frost for thirty years (since the age of about 20), it was only during the past two autumns that he has had asthma coming at the same time with the hay fever. However, during the past two winters he has had recurrences of asthma probably dependent on a chronic bronchial infection.

CASE 3.—This patient failed to give a positive skin test to any of seven different pollen extracts. She was susceptible to roses and her asthmatic attacks most commonly began in the mountains of New Hampshire in the summer, and were much worse during her three weeks' stay there. She has also had slight asthma at other times.

Treatment consisting of hypodermic injections of ragweed pollen has been carried out in only seven of these patients (Cases 2, 8, 32, 49, 106, 112 and 116), but it gave definite relief in five, and one case was practically entirely relieved.

CASE 2.—(Illustrates the importance of the skin test.) A girl, aged 23, had asthma for three years, much worse during June and August, but also at times during the winter. She also had hay fever and on this account was treated with ragweed pollen extract in spite of the negative skin test, but with almost no benefit. It is interesting to note in passing that she has *not* developed a positive skin test as a result of the treatment.

Twelve cases not classed as pollen asthma (Cases 5, 11, 15, 20, 35, 48, 80, 119, 123, 133, 144 and 150) gave a positive skin test to ragweed pollen. They are of special interest since none of them had hay fever nor increase of their asthma during the ragweed season. These cases show the necessity of agreement between skin test and history in order to prove the etiologic part played by pollen. It would be interesting to treat some of these cases to emphasize this point.

CASE 67.—(Closely related to this group.) A woman, aged 31, had asthma for two years and also had definite hay fever together with a positive skin test to ragweed pollen. She cannot be included in this group, because her asthma was not aggravated while the hay fever was in progress.

HORSE ASTHMA

Before taking up the clinical aspect of horse asthma, it is important to emphasize the observations of Walker,[32] Goodale,[30] Cooke,[29] and others on the definite anaphylactic specificity of horse hair protein and of horse serum.

As will be brought out in the following pages, thirty-seven patients gave a positive skin test to horse hair extract, whereas only six of these individuals gave a positive skin test to horse serum as well.

To test further the specificity of these two substances an attempt was made to sensitize guinea-pigs with one substance and shock them

with the other, but without positive results, as shown in Table 2. The horse hair extract used was the same extract used for the skin tests and contained in this test 2 mg. of nitrogen per cubic centimeter (100 times as much nitrogen per cubic centimeter as is used for skin tests).

This experiment shows the absence of any protein group-complex such as Wells[34] describes as theoretically responsible for some of the crossed anaphylactic reactions with various vegetable proteins, which might be common to horse serum and horse hair extract.

TABLE 2.—Anaphylactic Reactions of Horse Serum and Horse Hair Extract

Guinea-Pig No.	First Dose Intraperitoneal	Time Interval	Second Dose Intravenous	Result
1	1 c.c. horse hair extract	24 days	0.4 c.c. horse serum	No symptoms
2	1 c.c. horse hair extract	24 days	1 c.c. horse hair extract	Dead in 2 minutes
3	0.2 c.c. horse serum	24 days	1 c.c. horse hair extract	No symptoms
4	0.2 c.c. horse serum	24 days	0.5 c.c. horse serum	Dead in 2 minutes

Of the thirty-seven patients with positive tests to horse hair extract, sixteen were considered to have horse asthma. Thirteen of these gave a definite history of attacks occurring soon after coming near or remaining in contact with horses. All thirteen gave a markedly positive skin test to horse hair extract. For example:

Case 34.—A fireman was much affected by asthma until the former horse engine was replaced by a motor vehicle, whereupon his asthma definitely improved. Since that time, he occasionally is required to substitute at a station where they have horses and it is very instructive to learn that he becomes wheezy after being in this station *for twelve hours;* and again that this wheezing persists for about eighteen hours after he leaves the station.

This is a different story from that of the following patient:

Case 113.—A girl, aged 22, although brought up among horses in Texas, taking the full care of them and riding a great deal, had no trouble until after the age of 14. Ever since then, whenever she rides horseback, running of the nose, smarting and burning in the eyes begin in *a matter of minutes* and if the ride is a long one, definite asthma comes on and persists for an hour or two after the ride is over.

The time relations in these two cases are especially interesting and instructive. Do they show more than different degrees of sensitiveness?

34. Wells, H. G., and Osborne, T. B.: Biologic Reactions of the Vegetable Proteins, Jour. Infect. Dis., 1913, **12**, 341.

Three other patients who gave a positive skin test to horse hair gave also a history of asthma in attacks which were associated with different places and circumstances at least compatible with exposure to horses or other animals or to horse dust.

CASE 146.—A girl, aged 9, whose attacks came every other week, lasting one week, and who drove to school each day behind a horse.

CASE 61.—Who had asthma when living on a farm in winter.

CASE 58.—A girl, aged 10, who had asthma once a week which was definitely worse when the east wind blew toward her house from a stable across the way. The girl was somewhat improved on treatment with horse hair extract.

TABLE 3.—HORSE ASTHMA. SIXTEEN CASES

Case No.	Sex*	Present Age	Age at Onset	History	Skin Test to Horse Hair	Skin Test to Horse Serum	Skin Test to Dog Hair	Other Skin Tests	Results of Treatment With Horse Hair Extract	Family History	Eosinophilia, per Cent.	
											In Attacks	Between Attacks
4	♂	13	10	+	+	+	..	Rag. gold., aster	.....	+	.....	13.3
13	♂	38	8	+	+	+	+	Sera (R=o)	+	+	2	2.3
29	♀	31	3	+	+	0	..	Rag.	.....	+		
34	♂	25	22	+	+	0	..	..	.....	0	.....	11.4
45	♂	60	2	+	+	0	..	0	.....	+	5.3	
58	♀	10	4	±	+	+	..	0	.....	+	.....	4.3
61	♀	40	34	±	+	0	..	..	.....	0	.....	5
103	♀	33	18	+	+	+	+	..	++	+	8	3, 5.3
113	♀	22	14	+	+	0	+	..	++	0	.....	2.6
115	♀	45	21	+	+	0	..	Rag.	+	+	7.6, 4	
131	♀	23	18	+	+	0	..	Rag., grass?	.....	+	11	
132	♂	29	26	+	+	0	..	0	.....	..	.....	4.6
140	♀	17	15	+	+	+	..	Rag.	.....	+	.....	9
141	♀	48	28	+	+	0	..	Rag., grass, red top	+++	0	3.6	7.3
146	♀	9½	7	±	+	±	+	..	.....	0	7	
157	♂	28	1	+	+	+	..	Rag.	.....	+		

* ♂ = male; ♀ = female.

Of these sixteen patients, five have been under treatment with horse hair extracts, and all have been helped to a greater or lesser extent. Two of these patients, Cases 13 and 103, however, were the subject of a paper entitled "Interesting Reactions Obtained During Treatment of Two Cases of Bronchial Asthma,"[35] in which rather alarming even though transient anaphylactic responses were described.

35. Rackemann, F. M.: Interesting Reactions Obtained During Treatment of Two Cases of Bronchial Asthma, Jour. Am. Med. Assn., 1917, **69**, 889.

The other eleven have been told simply to avoid animals, and as a result most of them have remained comfortable. Table 3 gives a general summary of the cases in this group.

Besides these sixteen more or less clear cut cases of horse asthma, there are twenty-one cases who give a positive skin test to horse hair and yet do not give any history of horse susceptibility.

Eight of these have already been included under pollen asthma. They give skin tests to both ragweed and horse hair, but were classed as pollen cases because of the seasonal increase in their symptoms. Five more (Cases 30, 48, 66, 80 and 119) are discussed under "Bronchitis," two under "Tuberculosis" (Cases 74 and 96), two under "Gastro-Intestinal Asthma" (Cases 38 and 118), and four others are still unclassified (Cases 17, 63, 127 and 136). Two of these last are worthy of special mention.

Case 63.—A woman, aged 21, has had asthma every one to four weeks since infancy. These attacks come on at all seasons of the year. She repeatedly gave a positive skin test to horse hair extract. She has been followed for nearly a year. When first seen she cleared up rather promptly on five doses of the extract and then remained well for about three months (two months after the end of the treatment). She has asthma at the seashore; it came on again soon after her arrival, thus ending the three months period of freedom, and the asthma returned part of every week all summer. In the autumn, injections of horse hair extract were begun again, the improvement was not as marked as before, but she felt much relieved after each dose, so that now she returns to the hospital for treatment whenever she feels another attack is pending. She gives no history of being sensitive to horses. Her attacks are in no way associated with them and yet the injection of extract seems to have a definite effect. In this way, she seems to be an exception to the doctrine of the necessary positive history.

Case 136.—A man, aged 22, gave an intense reaction to horse hair extract and also to ragweed. He had typical hay fever from early August until frost for four years, and in the past four years had asthma. But this asthma comes on at any time of year, often when snow is on the ground and is, therefore, not a true pollen asthma. No focus of infection was found after careful search, and his family history was negative. His eosinophils were 6 per cent. In view of the skin test, he was given repeated doses of horse hair extract, but with no result whatever. He repeats the assertion that he is not affected by horses and can go into a stable without difficulty; so that this positive skin test becomes merely an observation, the significance of which is as yet unknown.

Why these twenty-one cases should give a positive skin test to horse hair is quite unknown. Many of them gave the test with more than one extract of horse hair showing the probability of the reaction being really a specific one.

The results of treatment in Case 63 are very interesting, and according to other experience in this work, are distinctly unusual.

It should be emphasized again here that these horse hair extracts were tested on many more than twenty-one other patients who gave no reaction at all, so that the extract cannot be classed as an irritant *per se*.

ACUTE FOOD ASTHMA

Only two cases in this entire group of 150 cases of asthma gave a history of exquisite susceptibility to food.

In taking the histories of each of these 150 patients, special attention has been paid to the question of food poisoning. This attention was, to a large extent, because of the recent interest in the possible relation of the ingestion of many different foods to not only asthma in particular, but anaphylactic states in general. Furthermore, many of these patients have been treated by omitting various biologic groups of food in rotation but never with beneficial result.

CASE 41.—A medical student, aged 24, whenever he eats fish or shellfish of any kind has, within a few minutes, swelling of his lips and tongue which develops into a general urticaria and within from ten to fifteen minutes leads to sneezing and asthma. Skin test to fish extract is intensely positive. His sister has hay fever; his mother has gastro-intestinal upsets, nausea, vomiting and diarrhea from eating fish. It is interesting to note that he has no marked eosinophilia. Counts made on two occasions gave figures of only 4.6 per cent. and 2.3 per cent., respectively. He knows his trouble well and remains in every way in perfect health as long as he avoids fish.

CASE 117.—This case is less striking. A girl, aged 3 years, at the age of 9 months developed eczema and urticaria in attacks. It was later discovered that ingestion of eggs caused immediate vomiting and swelling of the mouth and some slight difficulty in breathing. This child gave a markedly positive skin test to a solution of egg-white. The father has urticaria after eating strawberries; the mother had an attack of urticaria seventeen years ago, cause unknown. As far as is known, this child did not receive any egg until the age of 2. Since the test, egg has been excluded from the diet, but the eczema still persists so that its cause is not yet known. Skin tests to animal serums and hairs; to ragweed pollen; to fish extract and to milk, were all negative.

With these two cases, the extrinsic causes of asthma as found in this study have been covered. A total of forty-two cases, or only 28 per cent. of the whole number.

Intrinsic causes of asthma acting from within the body, as opposed to extrinsic causes—acting on the body from without, are now to be discussed.

GASTRO-INTESTINAL

In five patients, derangements of the gastro-intestinal tract seem to be a possible cause of their asthma.

CASE 38.—This patient had asthma for fifty-two years and maintains that any rich food which causes indigestion will precipitate an attack. He gives a positive skin test to horse hair and ragweed. He had "hay fever" all the year round up to ten years ago, which stopped with an operation on his nose, but asthma still continues.

CASE 122.—There is a history suggesting peptic ulcer and roentgenograms revealed a small ulcer in the region of the pylorus. Although he had a very light attack of difficult breathing nine years ago, he was free of asthma until about the time that his stomach began to trouble him. He also had an

emphysematous chest. Skin tests, family history, eosinophil counts and the search for various foci of infection were all negative. A five-meal diet with occasional doses of soda have relieved him, but he still has asthma.

CASES 52 AND 159.—These patients, aged 8 and 12, respectively, were relieved when meat was reduced in their diet.

CASE 118.—This patient has been studied carefully. A man, aged 30, has had asthma in weekly attacks for two years. There is no evidence of anaphylaxis except for an unexplained skin test to horse hair. There was no family history and no eosinophilia. Change of residence has not helped his asthma. Treatment of obstinate constipation relieved his asthma markedly when first seen, so that he had no bad attacks for two months, but he relapsed again. A second examination by the roentgen rays revealed a definite abscess at the roots of two teeth, a normal gastro-intestinal tract, normal nasal sinuses, but in the roentgenogram of the chest, there was a mottling along the markings, especially those running to the apices and shadow of the hylus which was unusually large.

Perhaps a tuberculosis of his bronchial glands was the true diagnosis, but if so, why the attacks and especially the two months period of freedom?

The possibility that, in some cases, disturbances of the metabolism of one of the three great classes of food might be at fault, must be considered. When, for example, asthma may be due, not to one particular protein, but to proteins, or, perhaps, carbohydrates or fats in general, as a class. Examination of the stools might be a distinct help in these conditions.

ACUTE BRONCHITIS

Twenty-four cases of bronchial asthma have attacks in which a cough is a prominent symptom, which attacks come on at fairly long intervals, usually several weeks, and have absolutely no relation to season, locality, weather, or dietary indiscretion, although the attack usually begins with a "cold."

Physical examination of these patients shows during the attack, the lungs full of sibilant and sonorous râles, but there is little change in the character of the breathing. Usually there are a few fine moist râles present in the bases. No other pathologic change has been made out; nothing appears on special examination of the nose and throat, and a roentgenogram of the chest reveals at the most a "thickening of the lung markings." There is little or no fever during the attack.

Between attacks these patients are quite normal, and providing they avoid taking cold again and avoid undue exertion or exposure such as swimming in cold water, can do or eat almost anything without return of their symptoms.

As will be seen by the accompanying table (Table 4), out of twenty-four patients presenting this clinical picture, seven gave a skin test to ragweed and four to horse hair as well, and one to horse hair alone. Five were not tested at all. Explanation of these positive tests

TABLE 4.—Acute Bronchitis. Twenty-Four Cases

Case No.	Sex*	Present Age	Age at Onset	Interval of Attacks (Weeks)	Dura- of Attacks (Days)	Skin Test	Other Anaphylactic Reaction	Foci	History of Attacks Associated With	Family History	Eosinophilia, per Cent.	
											In Attacks	Between Attacks
18	♀	36	25	4-24	3-4 14-21	0	0	Teeth	"A cold" winter or summer	0	.....	1.6
24	♀	23	1½	8-12	4-42 av. 7	0	0	.....	Catemenia	0		
30	♀	41	17	8-250 av. 12	3-4	Rag.? H. H.?	0	.....	"A cold" (has nephritis)	0		
31	♀	52	5	24	3-4	0	0	0	"A cold"	0		
33	♂	47	40	24	3	0	0	T. B. ? teeth	Spring and fall; worse lately	0	.....	2.6
35	♂	9	1	6-24	1-7	Rag., clover	0	0	"A cold" winter or summer (old empyema)	0		
37	♀	22	21	4-12	1-5 lately steady	0	0	T. B.	"A cold"	0	14 21	11.3
40	♀	35	33	2-24	7-14 -120	0	Hay fever	Teeth	East wind, cold and damp weather	0	6 4.3	
42	♀	50	27	12-24	2-7	0	0	(?)	Abdominal pain; indigestion	+	1	
48	♂	31	29	1	1	Rag., H. H. R. T.	0	0	Weather changes	0		
51	♂	34	34	12	2-14	0	0	Teeth	"A cold"	0		
54	♂	7	5	8-12	4-5	0	0	Tonsils, posture	Suggests early tuberculosis (?)	0		
56	♀	10	5	1-12	1-2	...	0	Teeth	"A cold"	0	11	
57	♂	9	7	24	2-7 -75	...	0	Teeth	"A cold"	+	13.3 7	
66	♂	25	8	20	1-12	H. H.	0	Teeth	Spring and fall	...	.....	1.6
80	♂	34	21	2-3	1-3	Rag. H. H.	0	.....	"A cold"; recent pneumonia	0	.....	0
81	♂	19	18	24	3-4	...	0	0	(?)	0		
93	♀	17	9	2-4	1-2	...	0	Posture	(?)	0		
101	♀	40	35	1-8	7-14	Rag.	0	Teeth, constipation	(?)	0	.....	1.6
119	♂	38	30	1-8	2-6 hrs.	Rag. H. H. H. S.	0	0	(?)	+	.....	5.3
125	♀	43	15	52 April	2-3 -60	Rag.	0	0	(?)	0	13 12.3	
134	♂	22	14	8	4-5	...	0	Septum	"A cold"	0		
145	♂	9½	9	1-8	7	0	0	Teeth	"A cold"	0	.....	6.6
149	♂	26	18	24	3-14 -60	0	0	0	"A cold"	0		

* ♂ = male; ♀ = female.

is difficult. Suffice it to say that none of these patients had hay fever nor were any of them susceptible to horses as such, and furthermore their attacks came at irregular and odd intervals.

Only three patients had a positive family history.

Five of these patients (Cases 48, 93, 101, 119 and 145) differ from the others, because of the relatively short intervals between their attacks, but except for one (Case 48) the other four often went at at least from one to two months without an attack.

It will be observed that the duration of attacks was in only eight patients (Cases 18, 24, 37, 40, 57, 66, 125 and 149) ordinarily more than fourteen days, and of these eight, in at least four (Cases 37, 57, 125 and 149), it is only recently that the character of the attacks has changed from their former and original short duration.

In regard to the histories. Asthma was associated with "a cold" in twelve patients; with changes in weather, especially in the spring and autumn in three; often with catamenia in one; with indigestion in one, and with unknown circumstances in six.

It is of importance to note that only one of these patients (Case 40) gave any history of hay fever; she gave no positive skin test and had this hay fever during only a period of five years ending four years ago.

Except for this one instance, there was no other evidence of any other anaphylactic manifestations, such as hay fever, hives or food poisoning in this group.

Since these twenty-four patients have attacks at such irregular intervals which do not correspond to any season, place, or circumstance, and since their skin tests seem to be, as far as we have gone, merely isolated observations it seems reasonable to assume that these patients suffer from the effects of something that they carry about with them; that their asthma is dependent on an intrinsic and not extrinsic cause. The theory that this intrinsic cause is a bronchitic infection is, of course, only a tentative explanation based on no definite grounds except the predominant cough and increase of expectoration; but, on the other hand, recurrent attacks of bronchitis are at least more common, in general, than similar recurrences of many other infections.

In the column headed "Foci" (Table 4) it will be seen that thirteen patients had a recognizable focus of infection. It does not seem likely that bad teeth, for example, could cause attacks of asthma at from 2 to 6 months intervals. True, the effect of extracting these teeth has, in most of these cases, not been studied. Two patients (Cases 33 and 37) showed signs at the lung apices suggesting tuberculosis, but it was finally agreed that these signs were not definite enough to warrant the diagnosis.

WINTER ASTHMA

In Osler's "Practice of Medicine," 1909, page 633, a description is given of emphysema which exactly fits a certain group of cases referred for "asthma." Little is known of the etiology of this group of cases, and they have been studied here, in the first place, to discover any possible etiologic relation to proteins, and in the second place, to see if they had anything in common, except difficulty in breathing, with other and more clear cut cases of asthma.

A brief description of these cases is a necessary repetition in order to define the object of study.

There is a group composed for the most part of older individuals whose asthma overtakes them with the onset of cold weather and they remain wheezy and short of breath, especially at night, until summer.

These cases give no skin tests to those foreign proteins of animal or vegetable origin which were tried. Their asthma is often severe and they can do little but sit quietly and try to breathe.

They present on examination very commonly a barrel chest, which is everywhere hyper-resonant so that the true heart borders are often obscured. They all have a peculiar "asthmatic" or nasal quality to their voice, a sign which is easily recognized, and often characteristic. Many of them raise considerable quantities of a white frothy sputum which usually contains numbers of eosinophilic leukocytes. At times the sputum is purulent and then contains a varied assortment of organisms in considerable quantities.

Asthma in these individuals is very much worse with any exertion, and if they can remain for a time quiet and especially in a warm atmosphere, their symptoms abate promptly.

Examination of the heart; determination of the blood pressure and examination of the urine have failed to reveal any important circulatory lesion in these cases. Most of them have emphysema and chronic bronchitis. In these patients potassium iodid usually gives great relief.

There are two fairly distinct groups of patients to whom the above description applies. They have been separated in this work, because while one group seemed to have asthma only in the winter and are quite normal in summer and warm weather, the other group has asthma off and one more or less continually throughout the twelve months. The first group has been styled "winter asthma" and includes here twelve cases.

As is shown on Table 5, five of these patients had asthma in very slight degree also at other times, but in the other seven, the asthma seemed limited to the cold weather. Eight out of the twelve had had bad teeth or trouble in the nose; one (Case 78) had her teeth extracted,

and another (Case 48) had her nasal polypi removed, but in neither case was there any permanent beneficial result to the asthma.

It will be observed that the age of onset in only two patients was below 25, and that the average for the whole group was 43.2 years — there being three patients whose asthma did not begin until after the age of 60. Skin tests were not done in five because these patients gave no history whatever which might suggest any extrinsic cause of their asthma. Those skin tests which were done were all negative in all patients.

TABLE 5.—Winter Asthma. Twelve Cases

Case No.	Sex*	Present Age	Age at Onset	Other Anaphylactic Reaction	Skin Tests	At Other Seasons	Foci	Family History	Eosinophilia, per Cent.	
									In Attacks	Between Attacks
6	♂	42	25	0	0	0	Eczema			
22	♂	74	70	0	0	±	0	0		
25	♂	64	62	0	0	±	Teeth	0	0, 1	
48	♀	40	38	0	...	0	Polypi	...	.....	2.3
65	♂	43	38	0	0	±	Nose, teeth	0	1.3	
78	♀	44	32	0	0	0	Teeth out	0	11.3	5.3
99	♂	36	34	0	0	±	Teeth	0		
100	♂	61	46	0	..	0	0	0		
102	♂	36	32	0	...	0	Teeth, constipation	0		
104	♂	47	47	0	...	0	Teeth	0	....	2.3
107	♀	36	24	0	...	0	Teeth			
148	♀	74	70	0	0	±	0	0	4	

* ♂ = male; ♀ = female.

Three patients (Cases 22, 25 and 148) should be really in a subgroup by themselves. In no one of them did asthma begin until after the age of 62. All three were elderly, tall, emaciated men with marked arteriosclerosis, with low blood pressure, clear, low gravity urines and regular pulses. All three were barrel chested with lungs full of squeaky râles, the breathing rather high pitched, prolonged and rather diminished in intensity. All three were slightly cyanotic. All three were helped to some extent by dram doses of a mixture of equal parts sodium bicarbonate and sodium phosphate which no doubt controlled the flatulency which, as Osler mentions, often accompanies emphysema. All three men were very uncomfortable; had to sit up in a chair practically all the time in winter, and often had to use most of the auxiliary muscles to breathe at all.

CHRONIC BRONCHITIS AND EMPHYSEMA

Except for the seasonal aggravation of their symptoms, these cases of winter asthma are in no way different from another group of cases which also have a chronic bronchitis as a basis for their asthma.

TABLE 6.—EMPHYSEMA AND CHRONIC BRONCHITIS. EIGHTEEN CASES

Case No.	Sex*	Present Age	Age at Onset	Other Anaphylactic Reaction	Skin Test	Foci	Lungs	Character of Attacks	Family History	Eosinophilia, per Cent.	
										In Attacks	Between Attacks
7	♂	46	45	0	0	.....	.....	Steady	0	12	
19	♀	28	10	0	...	.....	Bronchiectasis	Predominant cough	...	1.3	
28	♀	48	46	0	0	.....	Ch. Br.	Steady	0	2.3	
43	♂	50	45	0	0	.....	(Vaccines)	Steady for two years	0	0	
44	♂	48	48	0	0	0	Ch. Br.	Dyspnea on exertion	0	13 12.6 10.3	
47	♀	52	51	0	0	0	.....	Attacks at all seasons; steady	0	5	
64	♂	39	31	0	0	Nose	.....	Steady	0	3	
76	♂	33	31	0	0	Teeth antra	.....	Cough for two years; dyspnea on exertion	0		
85	♂	17	3	0	H. H.	.....	Ch. Br.	Growing worse, almost steady	0	3 1	
92	♂	48	41	0	0	Teeth	Ch. Br.	Worse in cold weather and on exertion	...	1.6	
94	♂	42	38	Hay fever	0	Teeth	.....	Steady, but worse on damp days	0	.....	1.3
97	♂	34	30	Urticaria	Rag.	Antra (vaccines)	.....	Constant wheeze; frequent cough; periodic attacks	0	3 3 5	
108	♂	45	30	0	0	Teeth	Ch. Br.	Steady	0		
111	♂	43	28	0	Rag. H. H.	.....	Ch. Br.	2-3 attacks a month lasting 2-3 days; weak spells; dyspnea on exertion	0	0 0	
154	♀	47	37	0	0	0	Heart?	Precordial pains; weak spells; dysp.	0	.....	14 10 9
20	♀	31	16	0	Rag.	0	Br. Glands, emphys.	Steady	...	4.3 1.3	
82	♀	54	44	0	0	Polypi removed 3 times	.....	Steady, every day for ten years	0		
160	♂	63	60	0	...	Teeth	Old tubere	Steady	0		

* ♂ = male; ♀ = female.

This latter group includes eighteen cases who have asthma practically steadily without much relation to season (Table 6). They too have emphysema and suffer often intensely from shortness of breath.

A careful history together with a careful examination fails to reveal any cause of asthma in these patients except the lung condition. Skin tests are nearly always negative. One patient had hay fever but the degree of asthma bore no relation to this and the hay fever had existed some years before the asthma appeared. Case 97 had urticaria (as described in the following pages). Aside from this, there was no history of susceptibility to proteins in the group.

Case 64.—This is a typical example. An Italian, aged 39, has had asthma for eight years practically every day. The asthma may stop suddenly in the middle of the day for an hour or so and then "he feels as good as any man." He was in the hospital ward for three weeks with little or no change in his condition and then his nose was operated on. Following a day or two of intense asthma, he began to improve somewhat, and though now some months afterward he still has asthma, he declares that he is "three times better than before."

Case 97.—This patient is interesting as showing the difficulties of treatment in these cases. He had bronchitis three years ago, which lasted two weeks and left him well; but eight months after this at the age of 30, he began to be wheezy and dyspneic. Since then he has had attacks every week or so which come on after eating or after exertion and last from one-half to three days. Except for one attack of urticaria four months ago, for which he can assign no cause, he has had no other manifestation of anaphylaxis. His eosinophils were never above 5 per cent.

Recently he has been observed on two occasions, two months apart, with a fever of 101 F., for which no cause has been found, but which came down after administration of salicylates. With this fever there was no special change in the asthma. His lungs show peculiarly loud wheezes throughout, which seem out of proportion to the degree of dyspnea. The roentgenogram suggests a diffuse bronchitis; no local focus was ever found in the lungs. Outside the hospital he has been given stock streptococcus vaccines, and these proving of no avail, he obtained an autogenous streptococcus vaccine from his sputum; doses of which were given every other day. As the doses were increased, he began to wheeze again and finally had a violent attack of asthma. His right antrum was cloudy and a roentgenogram revealed a possible infected root of a tooth, but neither of these foci was considered definite enough to warrant radical procedures. Changes in diet; first omitting all bread and all cereals for two months, and later omitting all meats, have given no results. Potassium iodid helps somewhat. Luckily his asthma is relatively mild.

Case 85.—This case is also typical of this group. The patient's history is given here in detail because of the very early age of onset.

A boy with asthma since the age of 3, but without any definite lesion to account for it. In the hospital he spent most of his time sitting on the edge of his bed breathing with difficulty—improvement was very slow. Inasmuch as there was nothing to go with it, the positive skin test to horse hair extract which was not marked was neglected. He had a typical emphysematous chest.

Two cases in this group show an eosinophilia.

Case 154.—This patient's history of precordial pains, and weak spells followed by dyspnea is not usual in asthma. Her chest was thick, hyper-resonant and there was prolonged expiration; she had an eosinophilia of 10 per cent. which so far is unexplained.

Case 44.—This patient also had a barrel-shaped chest with prolonged expiration. He had no hay fever or other obvious protein susceptibility. He had had symptoms for only a year and yet three blood smears taken on dif-

ferent occasions in a period of three months while his lungs were full of râles showed an eosinophilia of 13, 12 and 10 per cent., respectively.

The stools in both these patients were examined for parasites with negative results.

CASE 160.—This man, aged 63, has had asthma for only three years, and is another typical example of this group. He is of especial interest since he had tuberculosis fourteen years ago, with positive sputum and a tubercular laryngitis. At that time he was treated at the Rutland Sanatorium and in Colorado for two years and now presents only a healed process at the right apex. He had no asthma with this old tuberculosis.

A word should be said of the following case:

CASE 19.—A woman, aged 28, has had asthma since the age of 10, but in her case a cough was distinctly a prominent, if not predominant, feature. She raised considerable quantities of a greenish-yellow sputum, and roentgenogram revealed conditions quite typical of bronchiectasis.

Why should this woman among so many other cases of bronchiectasis have had attacks of shortness of breath?

It will be seen from Table 6 that two of these patients (Cases 64 and 82), with presumable lesions in the nose, had been operated on but without result.

TUBERCULOSIS

The association of asthma and tuberculosis has been discussed by O. Frankfurter[36] in 1913, who concluded that there was some causal relationship between them and who claimed that a systematic and long enough continued treatment with tuberculin may cause a diminution or cessation of the attacks.

Frenquelli[37] likewise had excellent results with tuberculin in two cases who had signs suggesting latent tuberculosis.

Giffin[38] saw eighty-two cases of spasmodic asthma, three of which had positive evidence of tuberculosis. During the same period he saw 226 cases of tuberculosis.

In this report it has seemed justifiable to include six cases under the diagnosis of tuberculous asthma, as shown in Table 7. Except for the two cases detailed in the following, the onset of asthma in these cases was quite coincident with the onset of the tuberculosis and on this account may be tentatively assumed to be dependent on it.

CASE 74.—A man, aged 59, has had asthma all his life with attacks spring and fall, but for the past two years has had it constantly; has lost 20 pounds in weight and although no tubercle bacilli could be found in his sputum, there were signs at both apices with a possible cavity in the left. The attacks

36. Frankfurter, O.: Asthma and Tuberculosis, Wien. klin. Wchnschr., 1913, **26,** 961.

37. Frenquelli, J.: Tuberculous Asthma; Two Cases, Semana Med., Buenos Aires, 1916, **23,** 583; Summarized in Jour. Am. Med. Assn., 1916, **68,** 1011.

38. Giffin, H. Z.: Asthma and Tuberculosis, Am. Jour. Med. Sc., 1911, **142,** 869.

up to two years ago were possibly due to pollen. Skin tests are suspicious and the patient stated that he had hay fever both spring and fall, for which he went up to Bethlehem, N. H., for relief. His tuberculosis, therefore, may have been an additional disease and not the cause of his attacks of dyspnea.

CASE 96.—This patient had a history of hay fever and stated that his asthma was worse on arrival in Nova Scotia late in August, and lasted throughout his stay. He was in the hospital ward in February, had a continuous fever and showed signs of consolidation in his lungs. He died in April presumably of tuberculosis, although no necropsy report is available. The late onset of his asthma (age 42) argues against a simple pollen asthma.

TABLE 7.—TUBERCULOSIS. SIX CASES

Case No.	Sex*	Present Age	Age at Onset	Evidence of Tuberculosis	Sputum	Sanatorium Treatment	Other Anaphylactic Reaction	Skin Tests	Family History	Eosinophilia, per Cent.	
										In Attacks	Between Attacks
74	♂	59	5	Lung sign	0	0	Hay fever	Rag. H. H.	0	4.6	
83	♂	32	19	Hemoptysis; lung sign	0	Rutland 13 years ago	0	...	0		
87	♂	37	27	Lung sign	+	Rutland 10 years ago	0	0	0	2.8	
90	♂	30	30	Lung signs; fever friction rub.	0	Rutland	0	...	0	10 8	
96	♂	45	42	Lung sign; irregular fever	...	.....	Hay fever	H. H.	+		
124	♀	26	26	Hemoptysis; lung sign	0	0	Hay fever				

* ♂ = male; ♀ = female.

Attention is also called to the following case:

CASE 160.—This patient (described under emphysema), had a positive tuberculosis, pulmonary and laryngeal, fourteen years ago, but *no asthma*, and now comes back with asthma dependent on emphysema and a chronic bronchitis, and presents no evidence of any active tuberculosis, although the right apex distinctly shows the old healed process.

NOSE AND TEETH

Four patients had lesions in the nose which were operated on, and to date the asthma in these patients has been helped (Table 8).

CASE 91.—This patient had very bad teeth, one of which had a pus pocket which was probably connected with the antrum, as removal of this tooth showed a long dirty root.

CASES 142 AND 158.—Both of these patients have emphysema. The former (Case 142) is interesting. Formerly his asthma came only in the summer, he had hay fever and today gives the corresponding skin tests. Now, however, his asthma has been steady until a marked improvement followed the nasal operation.

The latter (Case 158) was somewhat better after his operation but injections of a vaccine made from streptococci obtained from his antrum appear to have hastened this improvement markedly.

Throughout this communication references have been made to the nose and teeth as a cause of asthma. These four cases are the only ones in which the possibility of such an etiology as a very important factor, becomes a probability. It will be remembered that Walker[3] does *not* advise treatment of the nose, throat or teeth as a part of the treatment of asthma.

TABLE 8.—Nose and Teeth. Four Cases

Case No.	Sex*	Present Age	Age at Onset	Interval Between Attacks	Duration of Attacks	Other Anaphylactic Reaction	Skin Tests	Bad Teeth	Nose	Treatment	Family History	Eosinophilia, per Cent.	
												In Attacks	Between Attacks
91	♂	46	43	2-21 days	7-10 days	0	0	+	Antrum	Operd., slight result	0		
133	♂	28	5	1-7 days	1-2 days	0	0	0	Polypi	Tr. benzoin	0	9	
142	♂	60	10	†	†	0	Rag. grass	0	Polypi	Regular treat.	...	1 3	
158	♂	43	42	Steady	4 mos.	0	0	0	Artrum vaccines	Operd., no result	+	7	8 13

* ♂ = male; ♀ = female.
† Formerly only in summer, lately all the time.

MISCELLANEOUS

Under this head various other intrinsic causes are grouped together.

Bronchial Glands. — Roentgenograms of the chest have shown shadows near the roots of the lungs in many of these cases. In five of these cases, however, sufficient emphasis has been laid on these shadows in the interpretation of the plates to warrant special attention here. One of these patients (Case 20) has emphysema, and is placed in that group. Another (Case 36) has asthma only in summer, and is grouped under pollen asthma. This leaves then only three patients in whom it seems reasonable to assume that enlarged bronchial glands may be responsible for the asthma.

Case 89.—A boy, aged 16, thin, pale, and thick-chested, gave a history of asthma almost daily since babyhood. Skin tests, eosinophil counts and family history were negative, but the roentgenogram revealed large mediastinal glands.

Case 128.—A leather worker, aged 30, had asthma steadily for fifteen years, for which no other cause could be found except "a large mass of thick glands in the region of the hylus of the lung." Skin tests were negative. His asthma bore no relation to reason, locality or occupation. There was, however, a two year period of freedom ending three years ago.

Case 152.—This patient had had a cervical adenitis, probably tubercular, which makes the diagnosis in her case all the more plausible.

It is important that these three patients had asthma which was steady without distinct remissions. The two years freedom from asthma in Case 128 cannot be explained.

This persistent character of the asthma would naturally be consistent with a more or less permanent obstruction to the flow of air in the larger bronchi, or with irritation of the autonomic nerve supply to the bronchial muscles.

Lordosis.—One patient had this complication.

Case 39.—A stout Jewess, aged 42, has been relieved entirely of continued though mild asthma of four years' duration, by correcting a bad lordosis with a proper corset. Needless to say, her skin tests, family history, and eosinophil count were all negative.

Pregnancy.—Two women had asthma definitely associated with pregnancy.

Case 86.—This patient had intense asthma throughout her third pregnancy which disappeared a month after forced delivery at eight months. There was no asthma with her two earlier pregnancies. After delivery she had a constant eosinophilia of over 10 per cent.

Case 109.—Asthma occurred with her first and second pregnancies, seven and one year ago, respectively, but since then she has had asthma with changes of weather so that, recently at least, it may be due to some infection.

Catamenia.—In two other patients asthma was clearly associated with the catamenia.

Case 88.—She had attacks every four weeks for about five years.

Case 153.—This patient also had attacks closely associated with the catamenia, but these occasionally came at other times as after exposure, exertion, etc.

Circulatory.—In only two cases, could asthma be definitely ascribed to circulatory disturbances.

Case 129.—A woman, aged 50, had asthma for three years, acute attacks coming on from three to four times a year. Her heart was a trifle large; blood pressure, systolic 180, diastolic 100, and there were moist râles at the base of the lungs.

Case 130.—An obese Syrian woman, aged 29, had asthma for eight years with dyspnea on exertion between attacks; with edema of the ankles and some orthopnea. Little, however, was found on examination of the heart, blood pressure, or urine, to account for the trouble.

Even in these two cases the diagnosis of myocardial incompetency is, perhaps, open to doubt, and the asthma may well have been dependent on some other cause. As stated earlier, no cases with definite lesions readily demonstrable have been included in this report; consequently, cardiac asthma, as such, has not been considered.

UNCLASSIFIED

In this group are placed a number of cases, the causes of whose asthma are still unknown, either on account of as yet insufficient study or because a careful study has failed to disclose any etiologic factor which seemed to be reasonable. Included here are fourteen cases which have already been discussed in connection with other groups, but have been finally found not to belong in those groups This brings out the fact that in many cases the history and findings conflict in such a way as to leave the diagnosis much in doubt.

CASE 67.—This patient is discussed under pollen asthma.

CASES 63 AND 136.—Both are discussed under horse asthma.

CASES 73 AND 79.—In these cases no cause could be found. They had negative skin tests, doubtful family histories, and one of whom had an eosinophilia. They gave positive Wassermann reactions. Antisyphilitic treatment has, however, not been carried out so that the diagnosis of syphilitic asthma is not yet confirmed.

Five patients (Cases 1, 70, 71, 98 and 151) discussed under nervous asthma, should also be listed here, because in no one of them is a definite cause of their asthma proved or disproved.

Case 84, discussed under the subject of the effect of ether, also belongs here, as well as three cases given as part of six cases with eczema. In addition to this total of fourteen cases, there are still fifteen cases which are all represented on the accompanying Table 9. Three of these seem of sufficient interest to be detailed here, and their histories follow.

CASE 5.—A woman, aged 47, caught a cold eight years ago and had a mild attack of asthma for three weeks; this attack repeating itself every two or three months especially in winter, with comparative freedom between attacks. In the past three years, her asthma has been more or less constant and she has spent weeks at a time in bed, the same winter or summer. She gave a positive skin test to ragweed pollen but never had hay fever. She remained in the wards for two weeks and a half with asthma of severe type. Three days after an injection of 12.5 c.c. of her own defibrinated blood, she began to improve and with two other and larger doses, she left the hospital in ten days (November 19) with her lungs absolutely clear. She returned December 7, for 20 c.c. blood. December 13, she again had severe asthma. At her home, she was given 25 c.c. of her blood, which had absolutely no effect. On December 24, she struggled to the hospital, where the asthma continued unabated until January 11, during which time, she had five doses of her own blood. On this day, potassium iodid was given and she improved at once, and *has remained entirely well* for a period of eleven months. During her severe asthma, she had an eosinophilia of from 6 to 14 per cent. which disappeared with her improvement. It is, perhaps, important to note that she also suffered from arthritis which seemed to alternate with her asthma.

CASE 114.—A physician, aged 53, has had asthma since the age of 25. The attacks used to come on with his hay fever, but recently he has them constantly. A year ago he was in bed for six weeks with asthma. His pulse at that time

was intermittent and slow, but became very rapid on the least exertion. Lately, examination, even including roentgenograms of the chest, also an electrocardiogram, has failed to reveal any lesion. His breathing is not especially characteristic of emphysema. A lesion has lately been found in his nose, but has not yet been treated. Digitalis has not helped him.

TABLE 9.—Unclassified. Fourteen Cases (All Mentioned in Other Groups)

Case No.	Sex*	Present Age	Age at Onset	Other Anaphylactic Reaction	Skin Tests	Character of Asthma	Remarks	Family History	Eosinophilia, per Cent.	
									In Attacks	Between Attacks
67	♀	31	28	Hay fever	H. H. Rag.	Steady	"Pollen"	0	4, 1	
63	♀	21	1	0	H. H.	Every 1-4 weeks, ½-7 days	"Horse"	...	6	2, 6, 5
136	♂	22	18	Hay fever	H. H. Rag.	Slight attacks every 1-4 months, recently worse	.....	0	4.8	
73	♀	42	40	0	0	Steady	"Positive Wassermann"	...	8	
79	♂	24	14	0	H. H.	One night a week 2 years steadily	.....	...	...	1
1	♂	11	9	0	0	Every 1-3 weeks, lasting 1-3 days	"Nervous"	...	12.5	
70	♀	49	41	0	H. H. Rag.	Autumn for 5 yrs., steady for 3 yrs.	.....	0	1, 6, 1	
71	♂	29	22	0	0	Only in factory				
98	♂	21	6	0	H. H. Rag.	State of Maine	.....	0	1	
150	♀	10	9	0	H. H. Rag.	Only in Lynn, not in Salem	(Eczema)	0		
84	♀	30	28	0	0	Attacks at long intervals	Ovarian cyst and teeth	0	15.6	
123	♂	13	3	0	Rag. grass	Three days a week, same winter and summer	"Eczema"	0		
144	♂	7	7	0	Rag.	Steady for 1 month	"Eczema"	0	8.5	
151	♂	46	40	0	0	On shore, not at sea				

* ♂ = male; ♀ = female.

Case 156.—This case is of special interest. A professional masseuse, aged 29, drives about in a Ford automobile. After cranking the car, she enters and drives for about a minute, when severe asthma comes on and continues for over half an hour. If the Ford starts very easily, she has no trouble. Indoors, she can run up three flights of stairs without trouble. Careful physical examination by a leading clinician, roentgenograms of the chest and teeth, skin tests, special examination of nose and throat, all have been negative. At one time tuberculosis was suspected. Recently she has improved on 5 grains of calcium lactate, three times a day. How much of her asthma is "nervous"?

VARIOUS OTHER RELATED TOPICS

In addition to this detailed discussion incidental to the grouping of the individual cases, there are several interesting topics which are more or less related to the whole subject of asthma. Some of these which have come out in the study of these 150 cases as a whole are discussed here.

NERVOUS ASTHMA

Out of the total of 150 cases, there seemed to be at least six, in which the nervous or psychic element seemed to play an important part. These cases have each been studied carefully, and distinct effort has been made to account for their asthma otherwise. They are of importance, because if the diagnosis is really correct, some light may be thrown on the entire subject. Their histories are, therefore, detailed here.

CASE 1.—A boy, aged 11, had asthma for two years; his mother's mother is said to have had asthma. He had had asthma, coughing and dyspnea, every week or two for from one to three days at a stretch, with no relation to season or place. He remained in the hospital for two weeks, was up and about the ward, was eating a full house diet, and yet had absolutely no symptoms; all skin tests were repeatedly negative. The night after he went home he again had an attack. His home was investigated. The family had moved after his first year of asthma without result. Sleeping in different rooms, and on different beds and pillows, was of no avail.

He visited his father's mother, and was completely relieved as long as he stayed there. Her house was only a mile or two from his home, so that he attended the same school, and, as far as could be made out, ate the same sort of food. His teeth and throat were good. His posture was poor.

Was there something in his mother's house which caused his asthma, or was it dependent on a purely psychic disturbance, possibly due to his mother's overindulgence? Two findings are against the diagnosis of nervous asthma which otherwise seems necessary, the age of only 11, and the eosinophilia of 12 per cent.

CASE 150.—The case is of very much the same type. A girl, aged 10, has had a cough and been short of breath at night for a year. She sleeps poorly has enuresis and is constipated. She lives on a small truck farm where there are various animals and a small garden. As she gave a positive skin test to ragweed and to horse hair, her mother was advised to send the child to her grandmother's in the next town. A letter within three months afterward, states that the child is absolutely well and normal in every way. The asthma began two years before the family moved to the farm when they had no animals and no garden! The child was first seen late in October when true pollen asthma is over for the season.

CASE 70.—A woman, aged 49, had asthma dating from her arrival in San Francisco from Australia, at the age of 32. Her father's father had asthma, and a brother has hay fever. She came straight to Massachusetts and was well for eight years, when, at the age of 41, she suddenly began to have hay fever in August. The next year again hay fever, and this time asthma with it, and this combination has recurred each fall. Three years ago the asthma became chronic, and was so steady and so severe that she took morphin, and at the time of her admission to the hospital on March 3, 1917, was taking about 1½ grains daily. She entered the ward an emaciated, rather excited,

apprehensive, restless little woman, showing marked pigmentation, probably due to morphin.

She remained in the ward from March 3 until June 14, and throughout that long period she had to be given an average of about six doses of adrenalin chlorid in the twenty-four hours, to control her suffering.

She gave definite skin tests to ragweed, to horse hair, and to horse serum, but no tests to grass pollen. Treatment with horse hair extract was attempted, but after no result from five doses was abandoned. She was given four doses of her own defibrinated blood, with no result. Atropin, nitroglycerin, amyl nitrite, asthma powder, oxygen to inhale, pituitary extract were all tried, but in vain. Transfer to a private room made no difference. Eosinophils were found in her sputum, but in her blood were never over 6 per cent.

Special examination of teeth, sinuses, stools, etc., failed to reveal any cause for her troubles. The ragweed tests were discounted because of the time of year. Dr. W. H. Smith thought that "there is a very large nervous element in the case which probably accounts for most of the trouble."

She died on September 2, probably of inanition. There was no necropsy.

Two cases seemed associated with circumstances possibly disagreeable.

Case 71.—One of these was a medical student, aged 29, who had asthma for six years, only in isolated attacks, continuing from five to ten days, when he first begins his summer work in a shoe factory. It has never lasted longer than this, although he works in the same factory all summer. He has never had hay fever. Skin tests are absolutely negative. There is no trouble at other seasons of the year, and his family history is negative.

Case 151.—Another example may be a marine engineer, aged 46, who had asthma for six years, which came on only when he went ashore. He can go ashore and stay from four to five days without trouble, but if he has a cold he is sure to have asthma. If he has a cold at sea, he will never have asthma. This last fact argues against any infectious origin of his asthma, although his "colds" at sea may not be "colds" in the sense of a bacterial invasion.

EFFECT OF OPERATIONS UNDER ETHER

Three patients gave a history of previous operations under ether, following which there was in each case a distinct improvement in their asthma.

Case 15.—A woman, aged 38, who had asthma in attacks for four years, and in this work so far unclassified, had a tonsillectomy, within a year following which her asthma was indistinctly better for two or three months, but since then has been as bad as ever.

Case 125.—A woman, aged 43, had asthma since the age of 15; had several operations on her nose, and a year ago had the uterus and both ovaries removed. Her asthma improved for a time after this operation, and then relapsed. She is grouped here under "bronchitis."

Case 84.—A woman, aged 30, with asthma for two years, was found to have a rather large ovarian cyst. This was removed. Her asthma improved at once after the operation, and so remarkably that there seemed to be no doubt that the cause had been located. About a month after discharge from the hospital, she came in again with the same original symptoms.

It is, of course, unfortunate that skin tests were not made with the cyst fluid in Case 84. Had they been positive in her and negative

in a number of other control persons, important information would have been obtained.

It hardly seems reasonable to think, either in Case 125 or in Case 84, that the cause of the asthma was removed; the very fact that they relapsed again would show the cause to be still present. Why then, should they improve after the operation, and is it not reasonable to think that the administration of ether or the anesthesia itself, had some important effect? It would certainly be interesting to administer complete ether anesthesia to stubborn cases, such, for example, as Case 70. (Refer to the heading "Nervous Asthma.")

ECZEMA

Within the past two years interest has been shown in the possible explanation of eczema as a manifestation of anaphylaxis, and the association of eczema with asthma has, therefore, been studied in these 150 cases.

Blackfan[39] in studying eczema, finds that positive skin tests occur in the great majority of cases of eczema, while they occur only very rarely in the normal control.

He finds an early history of eczema in asthma patients, but he cannot prove the relation of eczema to anaphylaxis. He was unable to demonstrate circulating antibodies to the antigen in the blood serum of any patient giving a positive skin test to that antigen.

The relation of eczema to anaphylaxis is also mentioned by Schloss.[40]

Strickler and Goldberg[41] had twelve cases of eczema, six of which gave a positive skin test to one or more proteins.

Talbot[42] divides eczema in children into two groups, one of which depends on anaphylaxis.

White[43] also comments on the relationship of eczema to anaphylaxis.

In the present series, only six cases gave a history of eczema. Four of these were children (Cases 117, 123, 144 and 150), who had had eczema as babies, and three of whom had it with asthma. The fourth (Case 117) has had no further eczema, but asthma continues now for upward of nine years. Each of these four children gave one

39. Blackfan, K D.: Am. Jour. Dis. Child., 1916, **11,** 441.

40. Schloss, O. M.: Arch. Pediat., 1916, **33,** 210.

41. Strickler and Goldberg: Anaphylactic Food Reactions in Dermatology, Jour. Am. Med. Assn., 1916, **66,** 249.

42. Talbot: Tr. Am. Pediat. Soc., 1916, **28,** 190.

43. White, C. J.: Anaphylactic Phenomena in Eczema, Jour. Cutan. Dis., 1916, **34,** 55. The Treatment of Eczema in Childhood, Boston Med. and Surg. Jour., 1918, **178,** 5.

or more positive skin tests. Under "Diet" is a discussion of one of them (Case 117) in which the eczema was not influenced by the total omission of egg, to which alone of several proteins, she gave a skin test. The other three children reacted to the pollens, but the eczema was not worse in the autumn, and consequently the tests are disregarded.

Two patients (Cases 6 and 46) were adults, aged 43 and 40, respectively, with "winter" asthma for eighteen and two years, respectively, but they had had eczema for only six and one years. The connection between the asthma and eczema would, therefore, seem to be not a close one.

DISCUSSION

It is obvious that there are many different exciting causes of bronchial asthma. It is obvious that to discover the exciting cause in any patient requires considerable study, and finally, it is very striking to note that, in the whole series, there are no two cases which are even closely alike.

Separation of these patients into groups has been attempted and accomplished as accurately as possible. It often has been very difficult to group the individual patient, and he has been so grouped only when, after conscientious study, including as careful "following up" as was possible, it has seemed reasonable to do so.

A survey of 150 cases in this present report shows the following statistics: The age of the patients varies from 3 to 74, although there are only twenty-two patients who are below the age of 15. There were seventy-six males and seventy-four females. The onset of asthma occurred in the following age groups: Below 10, forty-two; between 10 and 20, twenty-eight; above 20, eighty; above 40, twenty-one.

Twenty-eight per cent. of the cases being classed as "extrinsic" is, apparently, a very small proportion. Perhaps further skin tests might have brought out further extrinsic causes. The possibility of susceptibility to feathers, to various dusts, powders and perfumes, and to various foods, has been kept constantly in mind, and yet it has not seemed reasonable to attribute the cause of asthma to these substances in any one of the 150 patients in this particular series.

These figures cannot well be compared with those of other authors because it is almost impossible to lay down definite criteria for the various groups. Careful consideration of the many factors has been the only means of classification. To see or to hear from the patient again after a period of several months has been a very great assistance in checking up the original impression and classification. Of 150 patients, all but twenty-six were seen more than once, twenty-five

patients have been followed for over a period of two months, thirty-three for over six months, and thirty-six for a period of over a year.

Table 10 represents a summary of the whole series. Aside from the eosinophil counts there are a number of striking observations. The average age at onset of extrinsic asthma is 12, or less than half the average age at onset of intrinsic asthma. There are about twice as many cases of intrinsic as of extrinsic asthma.

The family history is here very important and interesting. There was a history of either asthma, hay fever, hives or violent poisoning from food in forty-four of this group of patients; twenty-seven on the mother's side, and two on both; not stated in thirty-three. Fifty-eight percent. of the cases of extrinsic asthma gave a positive family history, while only 10.5 per cent. of the cases of intrinsic asthma gave such a history. Attention is here called to the figures of R. A. Cooke, who, as was stated, found a positive family history in 48.4 per cent. of his cases of sensitization, which may be compared to the 58.7 per cent. positive family history in cases of extrinsic asthma in this report.

From this we may say that a positive family history indicates the probability of a particular case of asthma belonging to the extrinsic rather than to the intrinsic group.

The most important problem in the study of asthma, and, at the same time, the one most difficult to approach, is, "Why are these people sensitive?" Effort has been made to discover whether there was any one factor common to all cases of asthma; some abnormality of anatomy or physiology present in these patients and not present in normal people. Such an abnormality would explain why certain individuals were susceptible to foreign proteins, and others were not.

The blood picture is one possibility inasmuch as an eosinophilia is said to occur commonly in asthma.

Differential blood counts have been done in 113 of these 150 patients; during the attacks in sixty-seven, and between the attacks in fifty-six, both in and between in twenty-one. In many patients several smears were counted.

According to Staubli[25] eosinophils decrease after the administration of adrenalin, but all cases are here included.

Total leukocyte counts were done in only twenty-two patients — a number too small from which to draw conclusions, except to show that, on the whole, the differential count gives a fair idea of the absolute numbers of these cells.

In nearly every smear 300 cells were counted. Wright's stain was used. Consideration of all these counts together shows that: during the attacks the eosinophils averaged 5.3 per cent.; between the attacks they averaged 5 per cent. (The patients were considered to be in an attack when sibilant râles were heard in the lungs.)

According to various textbooks, the normal percentage of eosinophils varies from 2 to 4 per cent. The percentage in asthma is, therefore, somewhat above the normal.

As is seen by Table 10, the averages, both for extrinsic and intrinsic asthma, are not very different. If anything, the counts made from patients with intrinsic asthma seem to be higher. Of more significance than this, however, is the absence of any important difference in the average of counts made during and between attacks.

In the twenty-one patients who were studied, both during and between the attacks, the eosinophils averaged 7.2 per cent. during the attacks (twenty-four smears) and 5.3 per cent. between attacks (twenty-four smears). Although in three patients the percentage of eosinophils was over twice as great between the attacks as during them.

Attention is also called to the columns on Table 10 showing the greatest percentage of eosinophils seen in the various groups. Here again, there is very little difference seen in counts made during and between attacks. In several cases counts were made at fairly frequent intervals during and after the attack, and no important and sudden change in the percentage of eosinophils at any particular time related to the attack was observed. It must be admitted, however, that not yet have sufficient observations been made on this point.

It may then be concluded that in human asthma there is no such constant variation in the percentages of eosinophilic leukocytes in the blood as is seen in experimental anaphylaxis in animals. The presence of an eosinophilia in asthma is confirmed, but its significance is not understood. Furthermore, it does not occur to a greater extent in those cases in which a resemblance to anaphylaxis exists, than in the others.

Further study is necessary before we can tell why these people are sensitive.

There is always a great temptation to regard asthma as an expression of some disturbance of the nervous system. This would explain the dissimilarity of the cases, even among those in the same group and would explain the behavior of many cases under circumstances which should theoretically have no significance. A few of the more striking examples have already been discussed under nervous asthma. But the great difficulty is that, on the other hand, there are many authentic cases, all with extrinsic asthma, who have had asthma come on when exposure to the antigen was sudden, and not at all anticipated, and there are many cases, some in this present series, in which a definite attack of asthma has been artificially produced by the injection of either ragweed pollen or horse hair extracts to which the patient was sensitive. It seems hard to explain how any "nervous" or any hysterical state, could explain this last condition.

TABLE 10.—SUMMARY OF THE WHOLE SERIES OF CASES

Group	Number Cases	Per Cent. Cases	Male	Female	Average Age at Onset	Average Duration in Years	Positive Family History in per Cent.	Eosinophilia							
								In Attack				Between Attacks			
								Number Cases Counted	Number Smears	Average Percentage	Greatest Percentage	Number Cases Counted	Number Smears	Average Percentage	Greatest Percentage
Pure pollen asthma	12	8	7	5	19.2	6.9	56	3	3	7	12	7	10	3	6.6
Complicated pollen asthma	12	8	5	7	3.2	8.4	45	7	13	5	10	8	10	5.3	10
Horse asthma	16	10.54	6	10	14.5	13.2	66	6	11	4.5	11	10	17	5.3	11
Acute food asthma	2	1.33	1	1	1.0	12.4	100	0	..	..	..	1	2	3.4	4.6
Summary extrinsic asthma	42	28	19	23	12.0	10.4	58.7	16	27	5	12	26	39	4.6	11.0
Gastrointestinal	5	3.33	5	0	19.0	14.4	0	3	4	4	4.6	2	2	3.5	4.0
Bronchitis	24	16	12	12	17.9	11.0	13	7	10	8.1	13.2	11	12	5.2	11.0
Winter asthma	12	8	9	3	43.2	6.7	10	4	5	3.6	11.3	3	3	3.3	5.3
Emphysema, chronic bronchitis	18	12	5	13	34.0	7.5	6.7	12	19	4.3	13	2	4	8.25	14.0
Tuberculosis	6	4	5	1	16.1	12.8	16.6	4	9	4.9	10	0			
Nose and teeth	4	2.66	4	0	25.0	19.25	0.6	3	4	5	9	1	2	10.5	13
Miscellaneous	10	6.66	2	8	23.8	6.7	11.1	6	8	6.25	13	4	6	4.8	12
Summary intrinsic asthma	79	52.64	42	37	26.05	9.86	10.5	37	59	5.4	13	23	29	5.5	14
Unclassified	29	19.36	15	14	21.3	9.2	28	14	20	5.3	15.6	7	10	4.4	11
Total	150	100	76	74	21.1	10.0	27.2	67	10.6	5.27	15.6	56	78	5.03	14

Attention is called to the fact that asthma has been already described[44] as one symptom of the condition known as vagotonia, in which there is a heightened tonus in the "vagal" or cranio-sacral autonomic system of nerves, and that another sign of this condition is an increase of the eosinophil cells. Further study on this point would be very important and might readily reveal that disturbance of physiology which theoretically is common to every case of the disease, and which would explain all forms of the disease which we now call bronchial asthma.

TREATMENT

The treatment of bronchial asthma resolves itself into the treatment of the exciting cause if this can be identified. The treatment of many individual cases has already been discussed in the body of the paper.

The best results are obtained in the cases of extrinsic asthma, especially in pollen cases. Treatment with an extract of the specific pollen will relieve the hay fever and the asthma often entirely. Specific treatment of the horse asthma cases is usually only partially successful, although the results obtained justify the effort.

The question of dosage as well as the time interval between doses is, of course, important but discussion of these factors must be based on a much larger series of cases. The general impression here has been that relatively small doses only sufficient to cause a noticeable local reaction on the arm persisting for twelve hours and given not more often than once in five days, has given the best result. The doses have been continued for at least twenty-five days after the asthma has abated.

Throughout this work the dosage has been measured in milligrams of total nitrogen — not in quantities of solutions.

There has been no experience with specific treatment of other extrinsic causes but avoidance of the particular protein has usually been possible and satisfactory.

The treatment of intrinsic asthma is far from satisfactory. Local treatment of the nose, throat and teeth has been long considered important. The removal of nasal polypi, the drainage of sinuses and the extraction of teeth will all relieve the asthma. This relief, however, rarely amounts to a cure and even if very marked is rarely permanent. The fact that many patients have spontaneous intervals of freedom from asthma which last for months or years, makes the results of any treatment difficult of interpretation.

The use of vaccines in the cases presumably due to bronchial infection whether or not these infections are accompanied by emphy-

44. Barker, L. F.: Canad. Med. Assn. Jour., 1913, **1.**

sema and the study of the bacterial flora in the sputum from these cases must be left for some future time.

In following these 150 cases, it has been a matter of the greatest interest to discover why periods of improvement have taken place. In most cases, no reason for this could be discovered. All of which suggests the marked nervous or autonomic element which doubtless exists. One patient who had been listed under chronic bronchitis and emphysema remained free of asthma, in spite of a continued cough for eleven months following exactly from the day of performing the various intradermal skin tests on his arm — which tests had been all negative.

Potassium iodid remains, as Lemann[45] puts it, the "sheet anchor" in the treatment of asthma. It is especially effective in cases whose asthma depends on a bronchitic infection.

Calcium salts were used in asthma by Kayser,[46] and in the present series have undoubtedly helped some cases.

Adrenalin is a very important drug in the treatment of asthma; a subcutaneous injection of adrenalin chlorid solution (Parke, Davis and Co.) will control the attack in almost every case. It, however, has relatively little effect on the general control of the disease. There is much literature on the use of adrenalin in asthma. The theories of its use are discussed by von Jagic.[47] Ephraim[48] has watched its effect through a bronchoscope. Staubli[49] recommends its use as a very fine spray and describes an atomizer for this purpose for which he claims more permanent results than by simpler methods of administration.

Asthma powders of various kinds, most of which contain niter and stramonium leaves, all help the attack, but do not cure. The treatment of associated conditions,[50] constipation, hyperacidity, etc., is always important, and the writer has seen more than one case very markedly improved on regular doses of a mild alkaline aperient salt.

Frequently unsuspected and apparently unimportant suggestions, such as a temporary change of residence, a slight temporary modification of the diet; ether anesthesia, temporary rest in bed with full diet, correction of faulty attitude, etc., have been of the greatest assistance, and not infrequently have led to a virtual cure. On all these various

45. Lemann, I. I.: Treatment of Bronchial Asthma, Am. Jour. Med. Sc., 1911, **142,** 781.
46. Kayser, C.: Therap. Monatsh., 1911, **26,** 157.
47. Von Jagic: Berl. klin. Wchnschr., 1909.
48. Ephraim: Deutsch. med. Wchnschr., 1912, **38,** 1453.
49. Staubli: München. med. Wchnschr., 1913, **60,** 113.
50. Ebstein, W.: Deutsch. med. Wchnschr., 1911, **38,** 1921.

methods there is rarely any good control, because so many patients have intervals of freedom from attacks, which intervals may last for several years.

CONCLUSIONS

1. "Bronchial asthma" is a symptom of some other diseased condition.

2. One hundred and fifty cases of asthma can nearly all be divided, according to the etiology of their attacks, into various subgroups under the general headings of "extrinsic asthma" and "intrinsic asthma."

3. Extrinsic asthma includes 28 per cent.; intrinsic asthma includes 53 per cent. of the entire group — the other 19 per cent. being unclassified.

4. The age at onset of extrinsic asthma averages about 12 years, while the age at onset of intrinsic asthma averages about 26 years.

5. A history of either asthma, hay fever or food poisoning, in the immediate family, occurs in 58.7 per cent. of the cases of extrinsic asthma, but in only 10.5 per cent. of the cases of intrinsic asthma.

6. Skin tests are of great assistance in confirming the diagnosis.

7. Skin tests alone are of no value unless reasonably compatible with the patient's history or experience.

8. A positive skin test is a necessary preliminary to successful specific treatment.

9. The "nervous" element is very important in asthma, but probably does not explain why certain individuals have asthma.

10. The percentage of eosinophilic leukocytes in the blood is increased in asthma; the degree of this increase is not different in extrinsic or intrinsic asthma, nor does it vary during and between the attacks.

11. Treatment resolves itself into the treatment of the exciting cause. Various different therapeutic procedures sometimes yield favorable results, but these cannot be explained.

12. The real problem — what is the fundamental disturbance of anatomy or physiology which expresses itself by attacks of asthma — remains unsolved.

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